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(57) Abstract

The present invention relates, in general, to a method of modulating physiological and pathological processes and, in particular, to a method of modulating cellular levels of oxidants and thereby processes in which such oxidants are a participant. The invention also relates to compounds and compositions suitable for use in such methods.

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SUBSTITUTED PORPHYRINS

TECHNICAL FIELD

The present invention relates, in general, to a method of modulating physiological and pathological processes and, in particular, to a method of modulating cellular levels of oxidants and thereby processes in which such oxidants are a participant. The invention also relates to compounds and compositions suitable for use in such methods.

BACKGROUND

Oxidants are produced as part of the normal metabolism of all cells but also are an important component of the pathogenesis of many disease processes. Reactive oxygen species, for example, are critical elements of the pathogenesis of diseases of the lung, the cardiovascular system, the gastrointestinal system, the central nervous system and skeletal muscle. Oxygen free radicals also play a role in modulating the effects of nitric oxide (NO·). In this context, they contribute to the pathogenesis of vascular disorders, inflammatory diseases and the aging process.

A critical balance of defensive enzymes against oxidants is required to maintain normal cell and organ function. Superoxide dismutases (SODs) are a family of metalloenzymes that catalyze the intra- and extracellular conversion of O_2^- into H_2O_2 plus O_2, and represent the first line of defense against the detrimental effects of superoxide radicals. Mammals produce three distinct SODs. One is a dimeric copper- and zinc-containing enzyme (CuZn SOD) found in the cytosol of all cells. A second is a tetrameric manganese-containing SOD (Mn SOD) found within mitochondria, and the third is a tetrameric, glycosylated, copper- and

zinc-containing enzyme (EC-SOD) found in the extracellular fluids and bound to the extracellular matrix. Several other important antioxidant enzymes are known to exist within cells, including catalase and glutathione peroxidase. While extracellular fluids and the extracellular matrix contain only small amounts of these enzymes, other extracellular antioxidants are also known to be present, including radical scavengers and inhibitors of lipid peroxidation, such as ascorbic acid, uric acid, and α-tocopherol (Halliwell et al, Arch. Biochem. Biophys. 280:1 (1990)).

The present invention relates generally to low molecular weight porphyrin compounds suitable for use in modulating intra- and extracellular processes in which superoxide radicals, or other oxidants such as hydrogen peroxide or peroxynitrite, are a participant. The compounds and methods of the invention find application in various physiologic and pathologic processes in which oxidative stress plays a role.

SUMMARY OF THE INVENTION

The present invention relates to a method of modulating intra- or extracellular levels of oxidants such as superoxide radicals, hydrogen peroxide, peroxynitrite, lipid peroxides, hydroxyl radicals and thiyl radicals. More particularly, the invention relates to a method of modulating normal or pathological processes involving superoxide radicals, hydrogen peroxide, nitric oxide or peroxynitrite using low molecular weight antioxidants, and to methine (ie, *meso*) substituted porphyrins suitable for use in such a method.

Objects and advantages of the present invention will be clear from the description that follows.

BRIEF DESCRIPTION OF THE DRAWING

Figures 1A-C show the structures of certain compounds of the invention. The SOD activity values were determined using the method of McCord and Fridovich, J. Biol. Chem. 244:6049 (1969). The catalase values were determined using the method of Day et al, Arch. Biochem. Biophys. 347:256 (1997). The TBARS values were obtained as follows:

Homogenates

Frozen adult Sprague-Dawley rat brains, livers and mouse lungs (Pel-Freez, Rogers, AR) were homogenized with a polytron (Turrax T25, Germany) in 5 volumes of ice cold 50 mM potassium phosphate at pH 7.4. Homogenate protein concentration was determined with the Coomassie Plus protein assay (Pierce, Rockford, IL) using bovine serum albumin as a standard. The homogenate volume was adjusted with buffer to give a final protein concentration of 10mg/ml and frozen as aliquots at -80°C.

Oxidation of homogenates

Microfuge tubes (1.5 ml) containing 0.2 ml of homogenate (0.2 mg protein) and various concentrations of antioxidant were incubated at 37°C for 15 minutes. Oxidation of the rat brain homogenate was initiated by the addition of 0.1 ml of a freshly prepared stock anaerobic solution containing ferrous chloride (0.25 mM) and ascorbate (1 mM). Samples were placed in a shaking water bath at 37°C for 30 minutes (final volume 1 ml). The reactions were stopped by the addition of 0.1 μL of a stock butylated hydroxytoluene (60 mM) solution in ethanol.

Lipid peroxidation measurement

The concentration of thiobarbituric acid reactive species (TBARS) in rat brain homogenates was used as a index of lipid peroxidation. Malondialdehyde

standards were obtained by adding 8.2 µL of 1,1,3,3-tetramethoxypropane in 10 ml of 0.01 N HCl and mixing for 10 minutes at room temperature. This stock was further diluted in water to give standards that ranged from 0.25 to 25 µM. Samples or standards (200 µL) were acidified with 200 µL of 0.2 M stock of phosphoric acid in 1.5 ml locking microfuge tubes. The color reaction was initiated by the addition of 25 µL of a stock thiobarbituric acid solution (0.11M) that was mixed and then placed in a 90°C heating block for 30 minutes. TBARS were extracted with 0.5 ml of n-butanol by vortexing for 3 minutes and chilling on ice for 1 minute. The samples were then centrifuged at 12,000 x g for 3 minutes and a 150 µL aliquot of the n-butanol phase was placed in each well of a 96-well plate and read at 535 nm in a Thermomax platereader (Molecular Devices, Sunnydale, CA) at 25°C. Sample absorbances were converted to MDA equivalences (µM) by extrapolation from the MDA standard curve. None of the antioxidants at concentrations employed in these studies affected the reaction of MDA standards with thiobarbituric acid.

Statistical analyses

Data were presented as their means ± SE. The inhibitory concentration of antioxidants that decreased the degree of lipid peroxidation by 50% (IC_{50}) and respective 95% confidence intervals (CI) were determined by fitting a sigmoidal curve with variable slope to the data (Prizm, GraphPad, San Diego, CA). (See also Braughler et al, J. Biol. Chem. 262:10438 (1987); Kikugawa et al. Anal. Biochem. 202:249 (1992).)

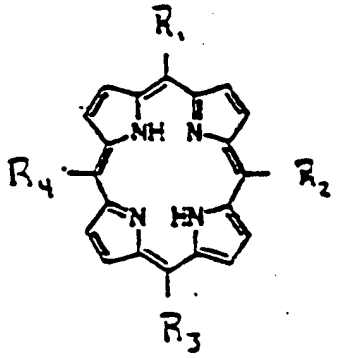
Figure 2 shows the data obtained from a study involving treatment of bronchopulmonary dysplasia using Aeol-V.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to methods of protecting against the deleterious effects of oxidants, particularly, superoxide radicals, hydrogen peroxide and peroxynitrite, and to methods of preventing and treating diseases and disorders that involve or result from oxidant stress. The invention also relates methods of modulating biological processes involving oxidants, including superoxide radicals, hydrogen peroxide, nitric oxide and peroxynitrite. The invention further relates to compounds and compositions, including low molecular weight antioxidants (eg - mimetics of scavengers of reactive oxygen species, including mimetics of SODs, catalases and peroxidases) and formulations thereof, suitable for use in such methods.

Mimetics of scavengers of reactive oxygen species appropriate for use in the present methods include methine (ie *meso*) substituted porphines, or pharmaceutically acceptable salts thereof (eg chloride or bromide salts). The invention includes both metal-free and metal-bound porphines. In the case of metal-bound porphines, manganic derivatives of methine (*meso*) substituted porphines are preferred, however, metals other than manganese such as iron (II or III), copper (I or II), cobalt (II or III), or nickel (I or II), can also be used. It will be appreciated that the metal selected can have various valence states, for example, manganese II, III or V can be used. Zinc (II) can also be used even though it does not undergo a valence change and therefore will not directly scavenge superoxide. The choice of the metal can affect selectivity of the oxygen species that is scavenged. Iron-bound porphines, for example, can be used to scavenge $NO\cdot$ while manganese-bound porphines scavenge $NO\cdot$ less well.

The mimetics of the present invention are of the Formula I:

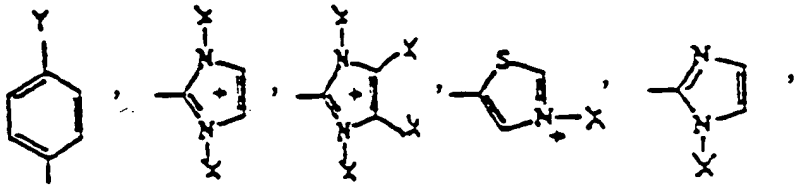


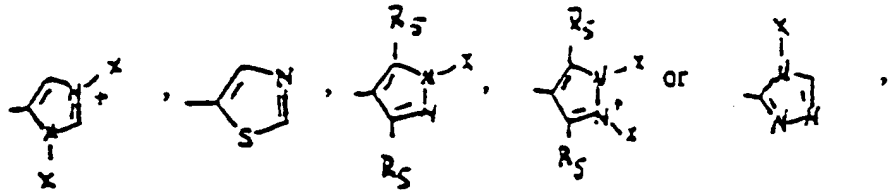
I

or pharmaceutically acceptable salt thereof

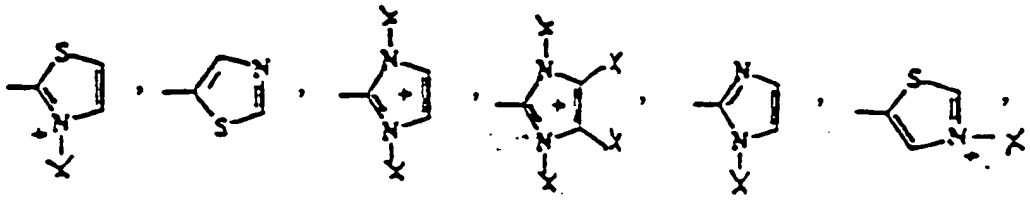
wherein:

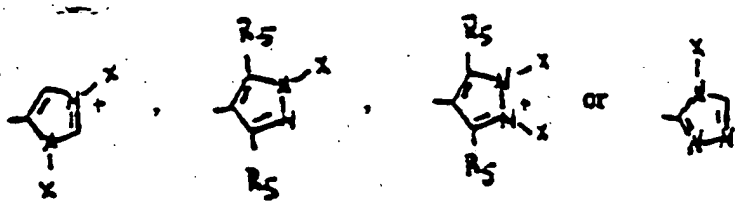
R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X 



R_2 and R_4 are the same and are :

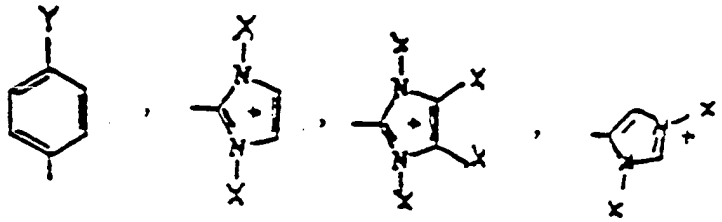


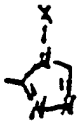


Y is halogen or $-CO_2X$,

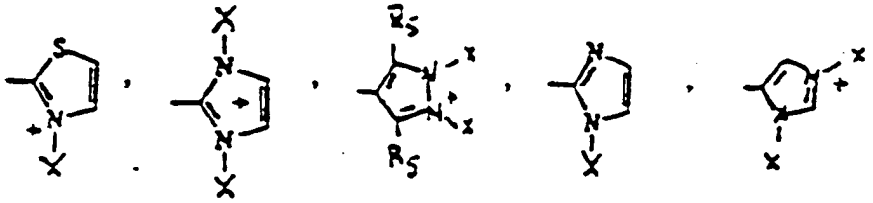
each X is the same or different and is an alkyl and each R_5 is the same or different (preferably the same) and is H or alkyl.

Preferably, R_1 and R_3 are the same and are:

-H, CF_3, $-CO_2-X$, 

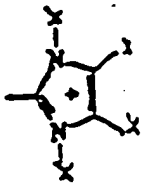
or 

R_2 and R_4 are the same and are :



Y is -F or $-CO_2X$

each X is the same or different and is an alkyl (preferably, C_{1-4} alkyl, e.g., methyl or ethyl) and each R_5 is the same or different (preferably the same) and is H or alkyl (preferably, C_{1-4} alkyl, e.g. $-CH_3$ or $-CH_2CH_3$).

Most preferably, R_1, R_2, R_3 and R_4 are the same and are  or  and each X is the same or different and is C_{1-4} alkyl, advantageously, methyl or ethyl, particularly, methyl.

Specific examples of mimetics of the invention are shown in Figure 1, together with activity data.

In addition to the methine (*meso*) substituents described above, one or more of the pyrrole rings of the porphyrin of Formula I can be substituted at any or all beta carbons, ie: 2, 3, 7, 8, 12, 13, 17 or 18. Such substituents, designated P, can be hydrogen or an electron withdrawing group. for example, each P can, independently, be a NO_2 group, a halogen (eg Cl, Br or F), a nitrile group, a vinyl group, or a formyl group. Such substituents alter the redox potential of the porphyrin and thus enhance its ability to scavenge oxygen radicals. For example, there can be 1, 2, 3, 4, 5, 6, 7, or 8 halogen (eg Br) substituents (preferably, 1–4), the remaining P's advantageously being hydrogen. When P is formyl, it is preferred that there not be more than 2 (on non-adjacent carbons), more preferably, 1, the remaining P's preferably being hydrogen. When P is NO_2, it is preferred that there not be more than 4 (on non-adjacent carbons), more preferably, 1 or 2, the remaining P's being hydrogen.

Where isomers are possible, all such isomers of the herein described mimetics are within the scope of the invention.

Mimetics preferred for use in the present methods can be selected by assaying for SOD, catalase and/or peroxidase activity. Mimetics can also be screened for their ability to inhibit lipid peroxidation or scavenge $ONOO^-$ (as determined by the method of Szabo et al, FEBS Lett. 381:82 (1996)).

SOD activity can be monitored in the presence and absence of EDTA using the method of McCord and Fridovich (J. Biol. Chem. 244:6049 (1969)). The efficacy of a mimetic can also be determined by measuring the effect of the mimetic on the aerobic growth of a SOD null *E. coli* strain versus a parent strain. Specifically, parental *E. coli* (AB1157) and SOD null *E. coli.* (JI132) can be grown in M9 medium containing 0.2% casamino acids and 0.2% glucose at pH 7.0 and 37°C; growth can be monitored in terms of turbidity followed at 700 nm. This assay can be made more selective for SOD mimetics by omitting the branched chain, aromatic and sulphur-containing amino acids from the medium (glucose minimal medium (M9), plus 5 essential amino acids).

Efficacy of active mimetics can also be assessed by determining their ability to protect mammalian cells against methylviologen (paraquat)-induced toxicity. Specifically, rat L2 cells grown as described below and seeded into 24 well dishes can be pre-incubated with various concentrations of the SOD mimetic and then incubated with a concentration of methylviologen previously shown to produce an LC_{75} in control L2 cells. Efficacy of the mimetic can be correlated with a decrease in the methylviologen-induced LDH release (St. Clair et al, FEBS Lett. 293:199 (1991)).

The efficacy of SOD mimetics can be tested *in vivo* with mouse and/or rat models using both aerosol administration and parenteral injection. For example, male Balb/c mice can be randomized into 4 groups of 8 mice each to form a standard 2X2 contingency statistical model. Animals can be treated with either paraquat (40 mg/kg, ip) or saline and treated with SOD mimetic or vehicle control.

Lung injury can be assessed 48 hours after paraquat treatment by analysis of bronchoalveolar lavage fluid (BALF) damage parameters (LDH, protein and % PMN) as previously described (Hampson et al, Tox. Appl. Pharm. 98:206 (1989); Day et al, J. Pharm. Methods 24:1 (1990)). Lungs from 2 mice of each group can be instillation-fixed with 4% paraformaldehyde and processed for histopathology at the light microscopic level.

Catalase activity can be monitored by measuring absorbance at 240nm in the presence of hydrogen peroxide (see Beers and Sizer, J. Biol. Chem. 195:133 (1952)) or by measuring oxygen evolution with a Clark oxygen electrode (Del Rio et al. Anal. Biochem. 80:409 (1977)).

Peroxidase activity can be measured spectrophotometrically as previously described by Putter and Becker: Peroxidases. In: Methods of Enzymatic Analysis, H.U. Bergmeyer (ed.), Verlag Chemie, Weinheim, pp. 286-292 (1983). Aconitase activity can be measured as described by Gardner and Fridovich (J. Biol. Chem. 266:19328 (1991)). The selective, reversible and SOD-sensitive inactivation of aconitase by known O_2^- generators can be used as a marker of intracellular O_2^- generation. Thus, suitable mimetics can be selected by assaying for the ability to protect aconitase activity.

The ability of mimetics to inhibit lipid peroxidation can be assessed as described by Ohkawa et al (Anal. Biochem. 95:351 (1979)) and Yue et al (J. Pharmacol. Exp. Ther. 263:92 (1992)). Iron and ascorbate can be used to initiate lipid peroxidation in tissue homogenates and the formation of thiobarbituric acid reactive species (TBARS) measured.

Active mimetics can be tested for toxicity in mammalian cell culture by measuring lactate dehydrogenase (LDH) release. Specifically, rat L2 cells (a lung Type II like cell (Kaighn and Douglas, J. Cell Biol. 59:160a (1973)) can be grown in Ham's F-12 medium with 10% fetal calf serum supplement at pH 7.4 and 37°C;

cells can be seeded at equal densities in 24 well culture dishes and grown to approximately 90% confluence; SOD mimetics can be added to the cells at log doses (eg micromolar doses in minimal essential medium (MEM)) and incubated for 24 hours. Toxicity can be assessed by morphology and by measuring the release of the cytosolic injury marker, LDH (eg on a thermokinetic plate reader), as described by Vassault (In: Methods of Enzymatic Analysis, Bergmeyer (ed) pp. 118-26 (1983); oxidation of NADH is measured at 340 nm).

The mimetics of the present invention are suitable for use in a variety of methods. The compounds of Formula I, particularly the metal bound forms (advantageously, the manganese bound forms), are characterized by the ability to inhibit lipid peroxidation. Accordingly, these compounds are preferred for use in the treatment of diseases or disorders associated with elevated levels of lipid peroxidation. The compounds are further preferred for use in the treatment of diseases or disorders mediated by oxidative stress. Inflammatory diseases are examples, including asthma, inflammatory bowel disease, arthritis and vasculitis.

The compounds of the invention (advantageously, metal bound forms thereof) can also be used in methods designed to regulate $NO\cdot$ levels by targeting the above-described porphines to strategic locations. $NO\cdot$ is an intercellular signal and, as such, $NO\cdot$ must traverse the extracellular matrix to exert its effects. $NO\cdot$, however, is highly sensitive to inactivation mediated by $O_2^{\cdot}$ present in the extracellular spaces. The methine (*meso*) substituted porphyrins of the invention can increase bioavalability of $NO\cdot$ by preventing its degradation by $O_2^{\cdot}$.

The present invention relates, in a further specific embodiment, to a method of inhibiting production of superoxide radicals. In this embodiment, the mimetics of the invention (particularly metal bound forms thereof) are used to inhibit oxidases, such as xanthine oxidase, that are responsible for production of superoxide radicals. The ability of a mimetic to protect mammalian cells from

xanthine/xanthine oxidase-induced injury can be assessed, for example, by growing rat L2 cells in 24-well dishes. Cells can be pre-incubated with various concentrations of a mimetic and then xanthine oxidase (XO) can be added to the culture along with xanthine (X). The appropriate amount of XO/X used in the study can be pre-determined for each cell line by performing a dose-response curve for injury. X/XO can be used in an amount that produces approximately an LC_{75} in the culture. Efficacy of the mimetic can be correlated with a decrease in XO/X-induced LDH release.

The mimetics of the invention (particularly, metal bound forms thereof) can also be used as catalytic scavengers of reactive oxygen species to protect against ischemia reperfusion injuries associated with myocardial infarction, coronary bypass surgery, stroke, acute head trauma, organ reperfusion following transplantation, bowel ischemia, hemorrhagic shock, pulmonary infarction, surgical occlusion of blood flow, and soft tissue injury. The mimetics (particularly, metal bound forms) can further be used to protect against skeletal muscle reperfusion injuries. The mimetics (particularly, metal bound forms) can also be used to protect against damage to the eye due to sunlight (and to the skin) as well as glaucoma, cataract and macular degeneration of the eye. The mimetics (particularly, metal bound forms) can also be used to treat burns and skin diseases, such as dermatitis, psoriasis and other inflammatory skin diseases. Diseases of the bone are also amenable to treatment with the mimetics. Further, connective tissue disorders associated with defects in collagen synthesis or degradation can be expected to be susceptible to treatment with the present mimetics (particularly, metal bound forms), as should the generalized deficits of aging. Liver cirrhosis and renal diseases (including glomerula nephritis, acute tabular necrosis, nephroderosis and dialysis induced complications) are also amenable to treatment with the present mimetics (particularly, metal bond forms thereof).

The mimetics of the invention (particularly, metal bound forms) can also be used as catalytic scavengers of reactive oxygen species to increase the very limited storage viability of transplanted hearts, livers, lungs, kidneys, skin and other organs and tissues. The invention also provides methods of inhibiting damage due to autoxidation of substances resulting in the formation of O_2^- including food products, pharmaceuticals, stored blood, etc. To effect this end, the mimetics of the invention are added to food products, pharmaceuticals, stored blood and the like, in an amount sufficient to inhibit or prevent oxidation damage and thereby to inhibit or prevent the degradation associated with the autoxidation reactions. (For other uses of the mimetics of the invention, see USP 5,227,405). The amount of mimetic to be used in a particular treatment or to be associated with a particular substance can be determined by one skilled in the art.

The mimetics (particularly, metal bound forms) of the invention can further be used to scavenge hydrogen peroxide and thus protect against formation of the highly reactive hydroxyl radical by interfering with Fenton chemistry (Aruoma and Halliwell, Biochem. J. 241:273 (1987); Mello Filho et al, Biochem. J. 218:273 (1984); Rush and Bielski, J. Phys. Chem. 89:5062 (1985)). The mimetics (particularly, metal bound forms) of the invention can also be used to scavenge peroxynitrite, as demonstrated indirectly by inhibition of the oxidation of dihydrorhodamine 123 to rhodamine 123 and directly by accelerating peroxynitrite degradation by stop flow analysis.

Further examples of specific diseases/disorders appropriate for treatment using the mimetics of the present invention, advantageously, metal bound forms, include diseases of the cardiovascular system (including cardiomyopathy, ischemia and atherosclerotic coronary vascular disease), central nervous system (including AIDS dementia, stroke, amyotrophic lateral sclerosis (ALS), Parkinson's disease and Huntington's disease) and diseases of the musculature (including diaphramic

diseases (eg respiratory fatigue in chronic obstructive pulmonary disease, cardiac fatigue of congestive heart failure, muscle weakness syndromes associated with myopathies, ALS and multiple sclerosis). Many neurologic disorders (including epilepsy, stroke, Huntington's disease, Parkinson's disease, ALS, Alzheimer's and AIDS dementia) are associated with an over stimulation of the major subtype of glutamate receptor, the NMDA (or N-methyl-D-aspartate) subtype. On stimulation of the NMDA receptor, excessive neuronal calcium concentrations contribute to a series of membrane and cytoplasmic events leading to production of oxygen free radicals and nitric oxide (NO·). Interactions between oxygen free radicals and NO· have been shown to contribute to neuronal cell death. Well-established neuronal cortical culture models of NMDA-toxicity have been developed and used as the basis for drug development. In these same systems, the mimetics of the present invention inhibit NMDA induced injury. The formation of O_2^- radicals is an obligate step in the intracellular events culminating in excitotoxic death of cortical neurons and further demonstrate that the mimetics of the invention can be used to scavenge O_2^- radicals and thereby serve as protectants against excitotoxic injury.

The present invention also relates to methods of treating AIDS. The Nf Kappa B promoter is used by the HIV virus for replication. This promoter is redox sensitive, therefore, an oxidant can regulate this process. This has been shown previously for two metalloporphyrins distinct from those of the present invention (Song et al, Antiviral Chem. and Chemother. 8:85 (1997)). The invention also relates to methods of treating systemic hypertension, atherosclerosis, edema, septic shock, pulmonary hypertension, including primary pulmonary hypertension, impotence, infertility, endometriosis, premature uterine contractions, microbial infections, gout and in the treatment of Type I or Type II diabetes mellitus. The mimetics of the invention (particularly, metal bound forms) can be used to

ameliorate the toxic effects associated with endotoxin, for example, by preserving vascular tone and preventing multi-organ system damage.

As indicated above, inflammations, particularly inflammations of the lung, are amenable to treatment using the present mimetics (particularly, metal bound forms) (particularly the inflammatory based disorders of emphysema, asthma, ARDS including oxygen toxicity, pneumonia (especially AIDS-related pneumonia), cystic fibrosis, chronic sinusitis, arthritis and autoimmune diseases (such as lupus or rheumatoid arthritis)). Pulmonary fibrosis and inflammatory reactions of muscles, tendons and ligaments can be treated using the present mimetics (particularly metal bound forms thereof). EC-SOD is localized in the interstitial spaces surrounding airways and vasculature smooth muscle cells. EC-SOD and O_2^- mediate the antiinflammatory - proinflammatory balance in the alveolar septum. NO· released by alveolar septal cells acts to suppress inflammation unless it reacts with O_2^- to form $ONOO^-$. By scavenging O_2^-, EC-SOD tips the balance in the alveolar septum against inflammation. Significant amounts of $ONOO^-$ will form only when EC-SOD is deficient or when there is greatly increased O_2^- release. Mimetics described herein can be used to protect against destruction caused by hyperoxia.

The invention further relates to methods of treating memory disorders. It is believed that nitric oxide is a neurotransmitter involved in long-term memory potentiation. Using an EC-SOD knocked-out mouse model (Carlsson et al. Proc. Natl. Acad. Sci. USA 92:6264 (1995)), it can be shown that learning impairment correlates with reduced superoxide scavenging in extracellular spaces of the brain. Reduced scavenging results in higher extracellular O_2^- levels. O_2^- is believed to react with nitric oxide thereby preventing or inhibiting nitric oxide-mediated neurotransmission and thus long-term memory potentiation. The mimetics of the invention, particularly, metal bound forms, can be used to treat dementias and memory/learning disorders.

The availability of the mimetics of the invention also makes possible studies of processes mediated by $O_2^{\cdot-}$, hydrogen peroxide, nitric oxide and peroxynitrite.

The mimetics described above, metal bound and metal free forms, can be formulated into pharmaceutical compositions suitable for use in the present methods. Such compositions include the active agent (mimetic) together with a pharmaceutically acceptable carrier, excipient or diluent. The composition can be present in dosage unit form for example, tablets, capsules or suppositories. The composition can also be in the form of a sterile solution suitable for injection or nebulization. Compositions can also be in a form suitable for opthalmic use. The invention also includes compositions formulated for topical administration, such compositions taking the form, for example, of a lotion, cream, gel or ointment. The concentration of active agent to be included in the composition can be selected based on the nature of the agent, the dosage regimen and the result sought.

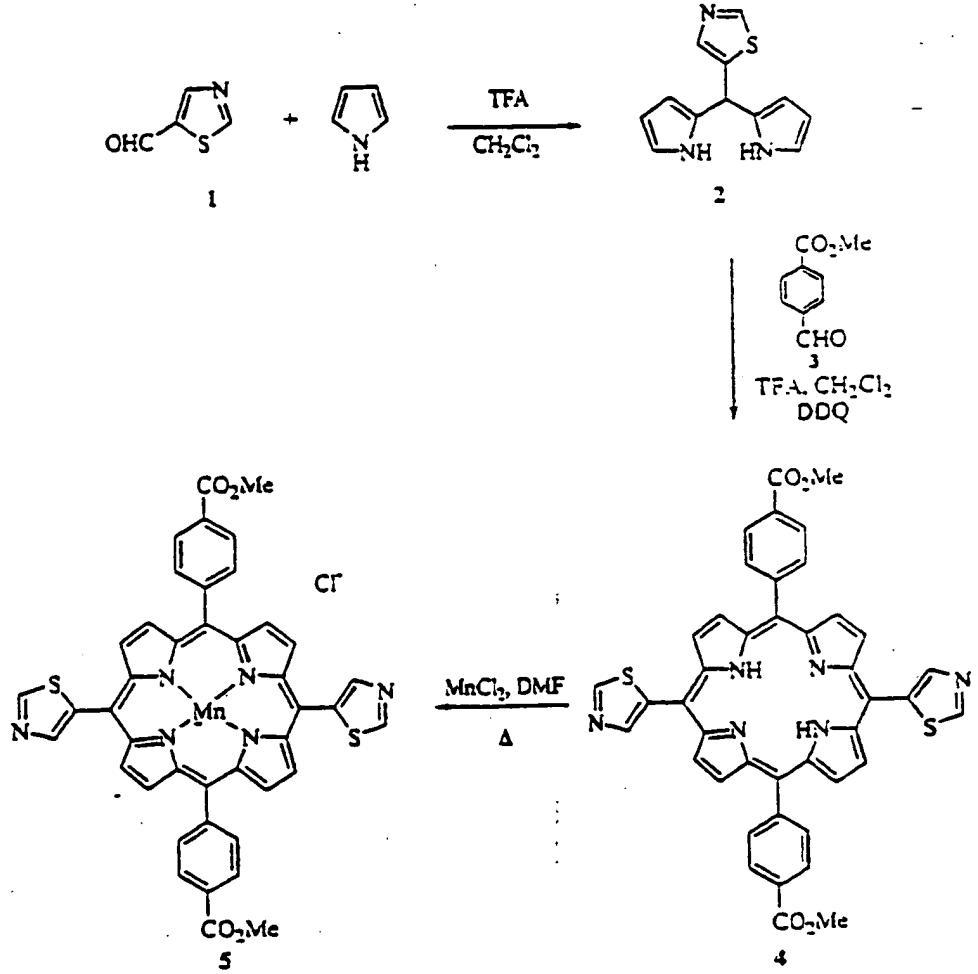
The dosage of the composition of the invention to be administered can be determined without undue experimentation and will be dependent upon various factors including the nature of the active agent (including whether metal bound or metal free), the route of administration, the patient, and the result sought to be achieved. A suitable dosage of mimetic to be administered IV or topically can be expected to be in the range of about 0.01 to 50 mg/kg/day, preferably, 0.1 to 10 mg/kg/day. For aerosol administration, it is expected that doses will be in the range of 0.001 to 5.0 mg/kg/day, preferably, 0.01 to 1 mg/kg/day. Suitable doses of mimetics will vary, for example, with the mimetic and with the result sought.

Certain aspects of the present invention will be described in greater detail in the non-limiting Examples that follow. (The numbering of the compounds in Example I is for purposes of that Example only.)

EXAMPLE I

Syntheses

I. [5,15-Bis(4-carbomethoxyphenyl)-10,20-(thiazol-5-yl)porphyrinato]-manganese(III) Chloride (5).



1. *meso*-(Thiazol-5-yl)dipyrromethane (2).

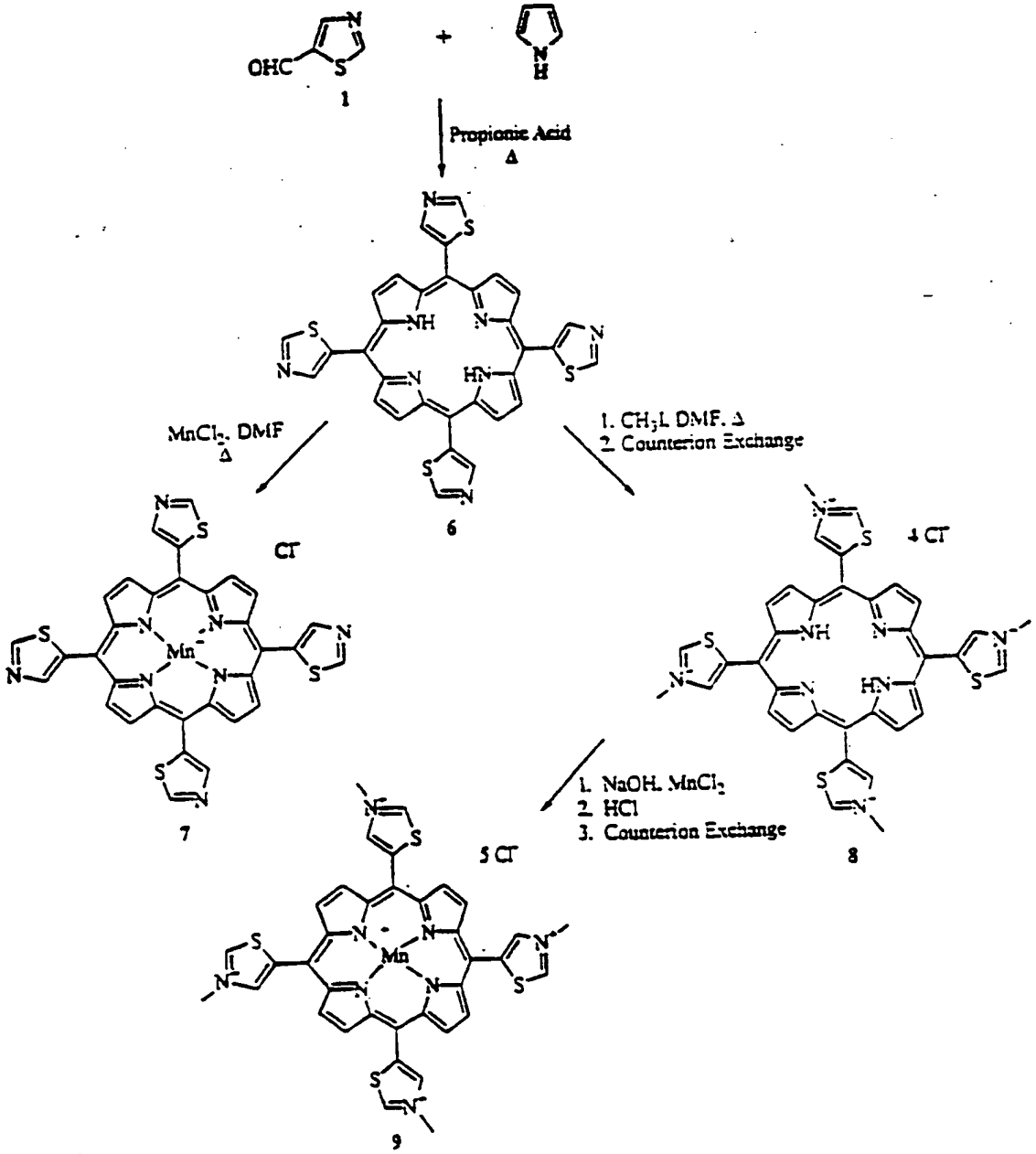
In a foil-covered 250-mL three-necked flask equipped with a magnetic stirrer and N_2 inlet, was placed 5-thiazolecarboxaldehyde (1, 0.88 g, 7.81 mmol) (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* 1987, 998-1001), CH_2Cl_2 (30 mL), and pyrrole (6 mL, 87 mmol). The reaction mixture was stirred for 10 min, then TFA (0.25 mL, 3.2 mmol) was added. After a stirring period of 2 h at room temperature, the reaction mixture was transferred to a separatory funnel and washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL) and adsorbed onto silica gel (3 g). Purification by column chromatography (gradient elution 33-67% EtOAc/hexanes) provided dipyrromethane 2 (0.95 g, 52%) as a gray solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1 H), 6.02 (m, 2 H), 6.17 (m, 2 H), 6.70 (m, 2 H), 7.58 (s, 1 H), 8.19 (br s, 2 H), 8.68 (s, 1 H).

2. 5,15-Bis(4-carbomethoxyphenyl)-10,20-(thiazol-5-yl)porphyrin (4).
In a foil-covered 250-mL three-necked round bottom flask equipped with a magnetic stirrer and a N_2 outlet, was added methyl 4-formylbenzoate (3, 180 mg, 1.09 mmol), dipyrromethane 2 (249 mg, 1.09 mmol), and CH_2Cl_2 (110 mL). The reaction mixture was stirred for 15 min, then TFA (0.25 mL, 3.25 mmol) was added. After a stirring period of 2.5 h at room temperature, DDQ (372 mg, 1.64 mmol) was added. The reaction mixture was stirred overnight and the solvent was removed *in vacuo*. The crude residue was adsorbed onto silica gel (3 g) then purified by column chromatography (gradient elution 0-1.5% MeOH/CH_2Cl_2) to provide porphyrin 4 (80 mg, 10% yield) as a purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ -2.75 (s, 2 H), 4.11 (s, 6 H), 8.28 (d, 4 H), 8.47 (d, 4 H), 8.65 (s, 2 H), 8.82 (d, 4 H), 8.99 (d, 4 H), 9.33 (s, 2 H).

3. [5,15-Bis(4-carbomethoxyphenyl)-10,20-(thiazol-5-yl)porphyrinato]-manganese(III) Chloride (5).

A solution of porphyrin 4 (75 mg, 0.101 mmol) and $MnCl_2$ (129 mg, 1.03 mmol) in DMF (15 mL) was heated at 125 °C for 14.5 h. The mixture was cooled to room temperature while exposed to a stream of air, then concentrated *in vacuo*. Repeated chromatographic purification of the product (gradient elution 5-10% MeOH/CH_2Cl_2) provided porphryin 5 (7 mg, 8%) as a dark green solid: mp >300 °C; UV-vis λ_{max} = 466.0 nm, $\varepsilon = 1.34 \times 10^5$ L/cm-mol; API MS *m/z* = 797 $[C_{42}H_{28}MnN_6O_4S_2]^+$.

II. [5,10,15,20-Tetrakis(thiazol-5-yl)porphyrinato]manganese(III) Chloride (7) and [5,10,15,20-Tetrakis(3-methylthiazolinm-5-yl)porphyrinato]-manganese(III) Pentachloride (9).



1. 5,10,15,20-Tetrakis(thiazol-5-yl)porphyrin (6).
A 250-mL three-necked flask equipped with a condenser and charged with propionic acid (60 mL) was heated to reflux. 5-Thiazolecarboxaldehyde (1, 373 mg, 3.30 mmol), pyrrole (230 μL, 3.32 mmol), and an additional 5 mL of propionic acid were added. After 3.5 h at reflux, the mixture was cooled to room temperature while exposed to a stream of air. The solvent was removed *in vacuo*, the residue was redissolved in $CHCl_3$/MeOH/concentrated NH_4OH (6:3:1; 100 mL), and the solvent was removed *in vacuo*. The residue was adsorbed onto silica gel (3 g) and purified by column chromatography (gradient elution, 1-2% MeOH/CH_2Cl_2) to provide porphyrin 6 (123 mg, 14%) as a solid: ^1H NMR (300 MHz, $CDCl_3$) δ -2.70 (s, 2 H), 8.67 (s, 4 H), 9.02 (s, 8 H), 9.38 (s, 4 H).

2. [5,10,15,20-Tetrakis(thiazol-5-yl)porphyrinato]manganese(III) Chloride (7).
A solution of porphyrin 6 (61 mg, 0.115 mmol) and $MnCl_2$ (144 mg, 1.14 mmol) in DMF (15 mL) was heated at 125 °C for 7.5 h. A stream of air was introduced and the reaction mixture was warmed to 130 °C. After a stirring period of 1.5 h, the reaction mixture was cooled to room temperature. The solvent was evaporated *in vacuo*, and the residue was adsorbed onto silica gel (2 g). Purification by column chromatography (gradient elution, 10-20% MeOH/CH_2Cl_2) provided porphyrin 7 (36 mg, 43%) as a dark green solid: mp >300 °C; UV-vis λ_{max} = 466.5 nm, ε = 3.55 x 10^4 L/cm-mol; FAB MS *m/z* = 695 $[C_{32}H_{16}MnN_8S_4]^+$.

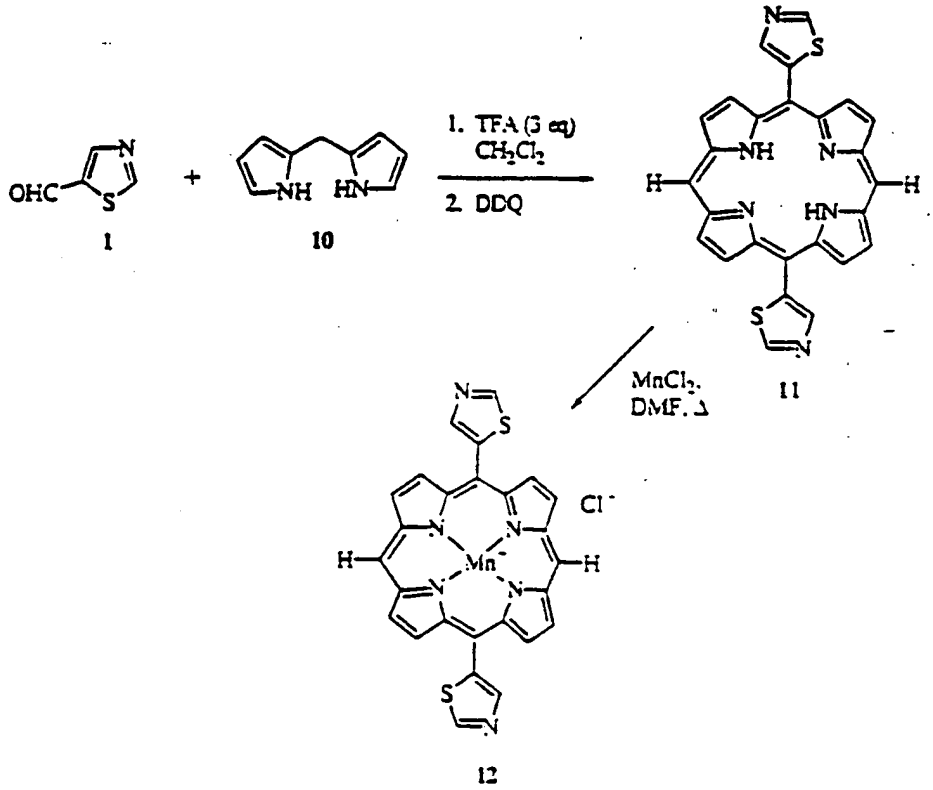
3. 5,10,15,20-Tetrakis(3-methylthiazolium-5-yl)porphyrin Tetrachloride (8).
A solution of 6 (123 mg, 0.19 mmol), CH_3I (5 mL), and DMF (5 mL) in a sealed tube was heated at 100 °C for 24 h. The crude porphyrin iodide salt that precipitated out of the reaction mixture was filtered, washed alternately with CH_2Cl_2 and ether, and dried under vacuum at room temperature. The iodide was dissolved

in water, precipitated out as the hexafluorophosphate salt (by dropwise addition of aqueous $NH_4^+PF_6^-$ solution; 1 g/10 mL), filtered, washed with water and isopropanol, and vacuum dried at room temperature. The hexafluorophosphate salt was dissolved in acetone then filtered (to remove insoluble solids). The product was precipitated out as the chloride salt from the filtrate by dropwise addition of a solution of $Bu_4NH_4^+Cl^-$ in acetone (1 g/10 mL), filtered, washed with copious quantities of acetone, and dried under vacuum at room temperature, to provide porphyrin 8 (66 mg, 41%): ^1H NMR (300 MHz, DMSO-d_6) -3.1 (s, 2 H), 4.6 (s, 12 H), 9.49 (s, 4 H), 9.58 (s, 8 H), 10.85 (s, 4 H).

4. [5,10,15,20-Tetrakis(3-methylthiazolium-5-yl)porphyrinato]manganese(III) Pentachloride (9).

Porphyrin 8 (60 mg, mmol) was dissolved in water (15 mL) and the solution pH was adjusted to pH = 12 by dropwise addition of 6N NaOH. Solid $MnCl_2$ (147 mg) was added into the reaction mixture (the resulting pH = 8.7). After a stirring period of 30-60 min, the reaction mixture was filtered through a fritted funnel lined with a filter paper. The pH of the filtrate was adjusted to pH = 4-5 (1N HCl) then the solution was filtered. Purification by the double precipitation method (as described for the preparation of 8) provided porphyrin 9
(6 mg, 8.2%) as a dark brown solid: mp >300 °C; UV-vis λ_{max} = 460.0 nm, ε = 1.25 x 10^5 L/cm-mol.

III. [5,15-Bis(thiazol-5-yl)porphyrinato]manganese(III) Chloride (12).



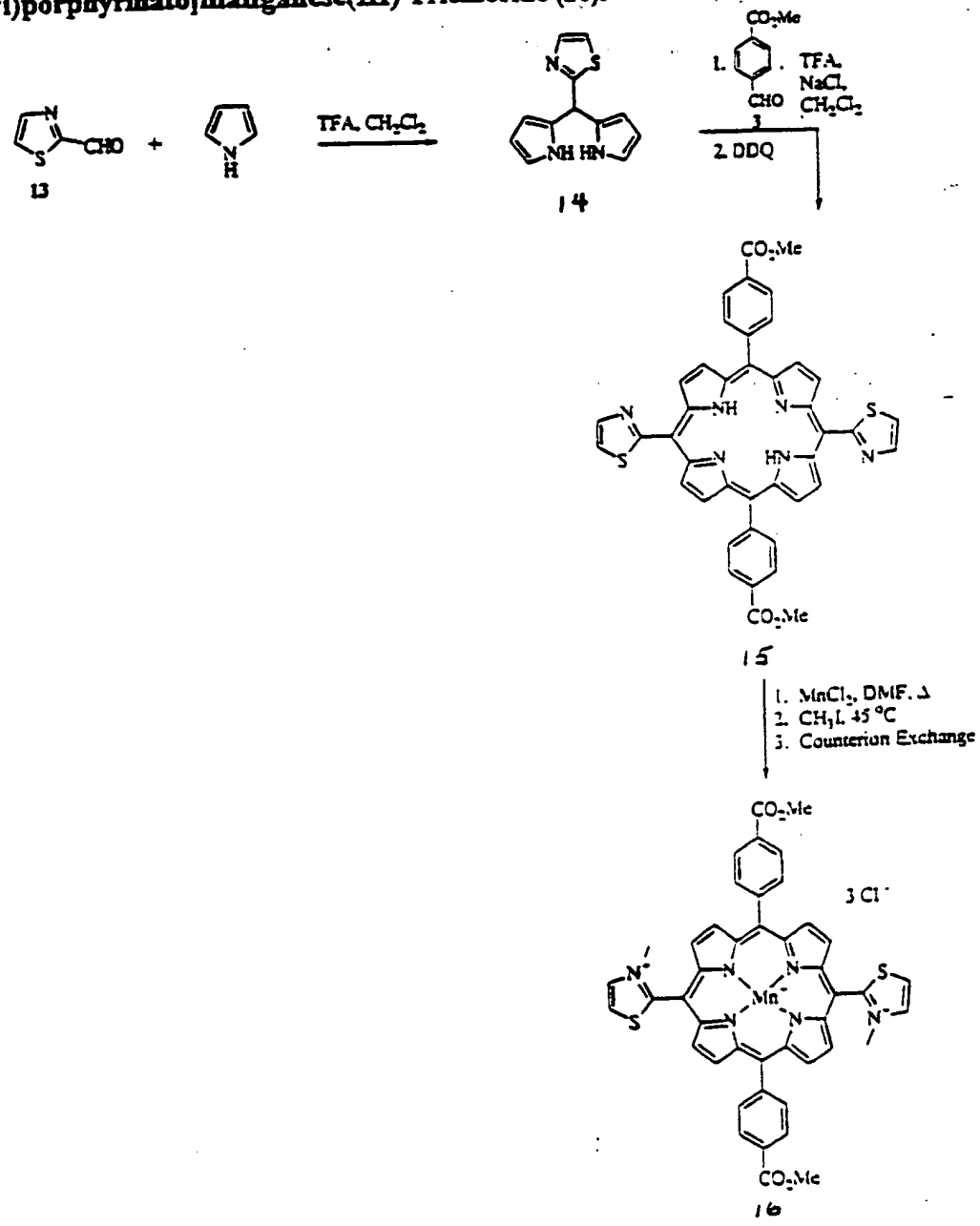
1. 5,15-Bis(thiazol-5-yl)porphyrin (11).

In a foil-covered 500-mL three-necked round bottom flask, equipped with magnetic stirrer and a N_2 inlet, was added dipyrromethane 10 (288 mg, 1.97 mmol) (Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229), 5-thiazolecarboxaldehyde (1, 223 mg, 1.97 mmol), CH_2Cl_2 (198 mL) and sodium chloride (13 mg, 0.2 mmol). The reaction mixture was stirred vigorously for 10 min, then TFA (0.46 mL, 5.97 mmol) was added. After a stirring period of 40 min, DDQ (671 mg, 2.96 mmol) was added, and the reaction mixture was stirred for an

additional 4 h. The solvent was evaporated *in vacuo*, and the residue was adsorbed onto silica gel (3 g). Repeated chromatographic purification (gradient elution 0.5-2% MeOH/CH_2Cl_2) provided porphyrin 11 (28 mg, 6%) as a solid: ^1H NMR (300 MHz, $CDCl_3$) δ -3.07 (s, 2 H), 8.69 (s, 2 H), 9.21 (d, 4 H), 9.39 (s, 2 H), 9.43 (d, 4 H), 10.35 (s, 2 H).

2. [5,15-Bis(thiazol-5-yl)porphyrinato]manganese(III) Chloride (12).
A solution of porphyrin 11 (28 mg, 0.0587 mmol) and $MnCl_2$ (85 mg, 0.675 mmol) in DMF (8 mL) was heated at 125 °C for 15 h. The mixture was cooled to room temperature while exposed to a stream of air, and the solvent was removed by rotary evaporation. The residue was dissolved in 10% MeOH/CH_2Cl_2 (50 mL) and adsorbed onto silica gel (500 mg). Purification by column chromatography (gradient of 5-10% MeOH/CH_2Cl_2) provided porphyrin 12 (29 mg, 86%) as a dark brown solid: mp >300 °C; UV-vis λ_{max} = 457.5 nm, ε = 3.75 x 10^4 L/cm-mol; API MS *m/z* = 529 $[C_{26}H_{14}MnN_6S_2]^+$.

IV. [5,15-Bis(4-carb methoxyphenyl)-10,20-bis(3-methylthiazolium-2-yl)porphyrinato]manganese(III) Trichloride (16).



1. *meso*-(Thiazol-2-yl)dipyrromethane (14).

In a foil-covered 250-mL three-necked flask, equipped with a magnetic stirrer and a N_2 inlet, was placed 2-thiazolecarboxaldehyde (13, 0.97 g, 8.6 mmol) (Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *Synthesis* **1987**, 998-1001), CH_2Cl_2 (35 mL), and pyrrole (7.2 mL, 104 mmol). The reaction mixture was stirred for 10 min, then TFA (0.26 mL, 3.4 mmol) was added. After a stirring period of 1 h at room temperature, the reaction mixture was transferred to a separatory funnel and washed with saturated aqueous $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 mL), and adsorbed onto silica gel (3 g). Purification by column chromatography (1:1 ether/hexanes) provided dipyrromethane 14 (1.22 g, 62%) as a solid: ^1H NMR (300 MHz, $CDCl_3$) δ 5.78 (s, 1 H), 6.04 (s, 2 H), 6.15 (m, 2 H), 6.71 (m, 2 H), 7.20 (d, 1 H), 7.74 (d, 1 H), 8.81 (br s, 1 H).

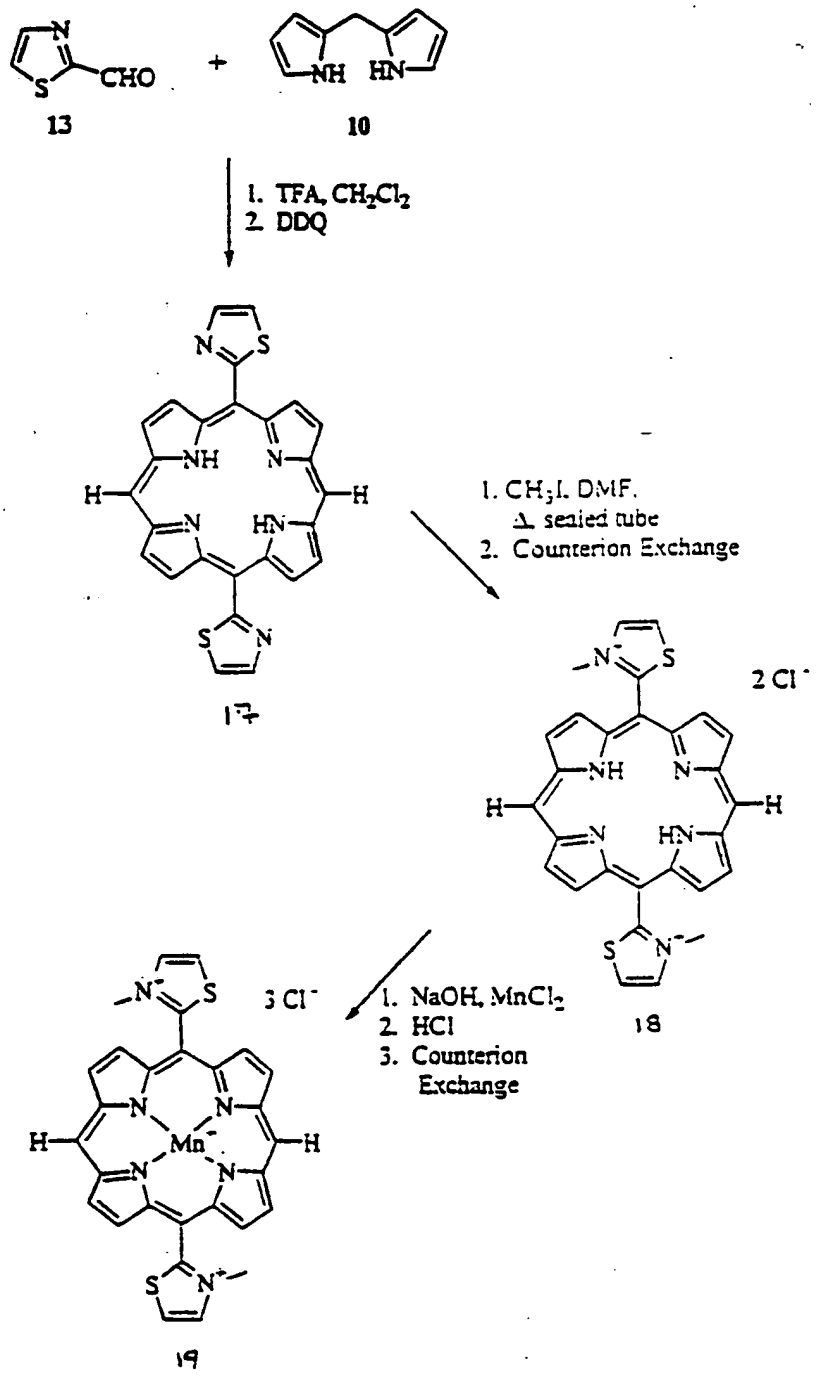
2. 5,15-Bis(4-carbomethoxyphenyl)-10,20-(thiazol-2-yl)porphyrin (15).

In a foil-covered 500-mL three-necked round bottom flask, equipped with a magnetic stirrer and a N_2 outlet, was added dipyrromethane 14 (771 mg, 3.39 mmol), methyl 4-formylbenzoate (3, 0.557 g, 3.36 mmol) and CH_2Cl_2 (350 mL). The reaction mixture was stirred for 15 min, then TFA (0.8 mL, 10.4 mmol) was added. After a stirring period of 3 h at room temperature, DDQ (1.16 g, 1.64 mmol) was added. The reaction mixture was stirred for 2 d, then the solvent was removed *in vacuo*. The residue was adsorbed onto silica gel (4 g) and purified by column chromatography (gradient elution 0.5-1% MeOH/CH_2Cl_2) to provide porphyrin 15 (140 mg, 11%) as a purple solid: (300 MHz, $CDCl_3$) δ -2.29 (s, 2 H), 4.12 (s, 6 H), 8.02 (d, 2 H), 8.30 (d, 4 H), 8.44 (d, 2 H), 8.47 (d, 4 H), 8.84 (d, 4 H), 9.05 (d, 4 H).

3. [5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(3-methylthiazolium-2-yl)-porphyrinato]manganese(III) Trichloride (16).

A solution of porphyrin 15 (26 mg, 0.054 mmol) and $MnCl_2$ (40 mg, 0.40 mmol) in DMF (20 mL) was heated at 135 °C overnight. The mixture was cooled to 45 °C and CH_3I (0.8 mL, 11.2 mmol) was added. The reaction mixture was stirred for 36 h at 45 °C and DMF was evaporated *in vacuo*. The residue was purified by column chromatography (gradient elution EtOAc, $CHCl_3$, MeOH, concentrated NH_4OH) to provide the product contaminated with impurities. Following a second purification by column chromatography (6:3:1 $CHCl_3$/MeOH/concentrated NH_4OH) non-polar fractions were collected leaving the bulk of product at the top of the column. The top silica gel containing the product was collected and washed with $CHCl_3$/MeOH/1N HCl (6:4:1). Evaporation of the acidic solution provided the product that contained excess inorganic salts. Purification by the double precipitation method and vacuum drying at 35 °C for 2 d provided porphyrin 16 (9 mg, 28%) as a black solid: mp >300 °C; UV-vis λ_{max} = 459.0 nm; $\varepsilon = 1.36 \times 10^5$ L/cm-mol; API MS *m/z* = 886 $[C_{44}H_{32}MnN_8O_4S_2{+}CH_3CO_2^-]^+$.

V. [5,15-Bis(3-methylthiazolium-2-yl)porphyrinato]manganese(III) Trichloride (19).


CHO
13
10
1. TFA, CH_2Cl_2
2. DDQ
17
1. CH_3I, DMF,
Δ, sealed tube
2. Counterion Exchange
2 Cl^-
18
3 Cl^-
1. NaOH, $MnCl_2$
2. HCl
3. Counterion Exchange
19

1. 5,15-Bis(thiazol-2-yl)porphyrin (17).

In a foil-covered 500-mL three-necked round bottom flask, equipped with magnetic stirrer and a N_2 inlet, was added dipyrromethane (**10**, 677 mg, 4.6 mmol), 2-thiazolcarboxaldehyde (**13**, 524 mg, 4.6 mmol), and CH_2Cl_2 (450 mL). The reaction mixture was stirred for 10 min, then TFA (1 mL, 16.9 mmol) was added. After a stirring period of 1 h, DDQ (1.58 g, 7 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated *in vacuo*, and the residue was adsorbed onto silica gel (3 g). Repeated purification by column chromatography (gradient elution 1-2% MeOH/CH_2Cl_2) provided porphyrin **17** (51 mg, 4.62%) as a purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ
-3.05 (s, 2 H), 8.06 (d, 2 H), 8.51 (d, 2 H), 9.35 (d, 4 H), 9.45 (d, 4 H), 10.40 (s, 2 H).

2. 5,15-Bis(3-methylthiazolium-2-yl)porphyrin Dichloride (18).

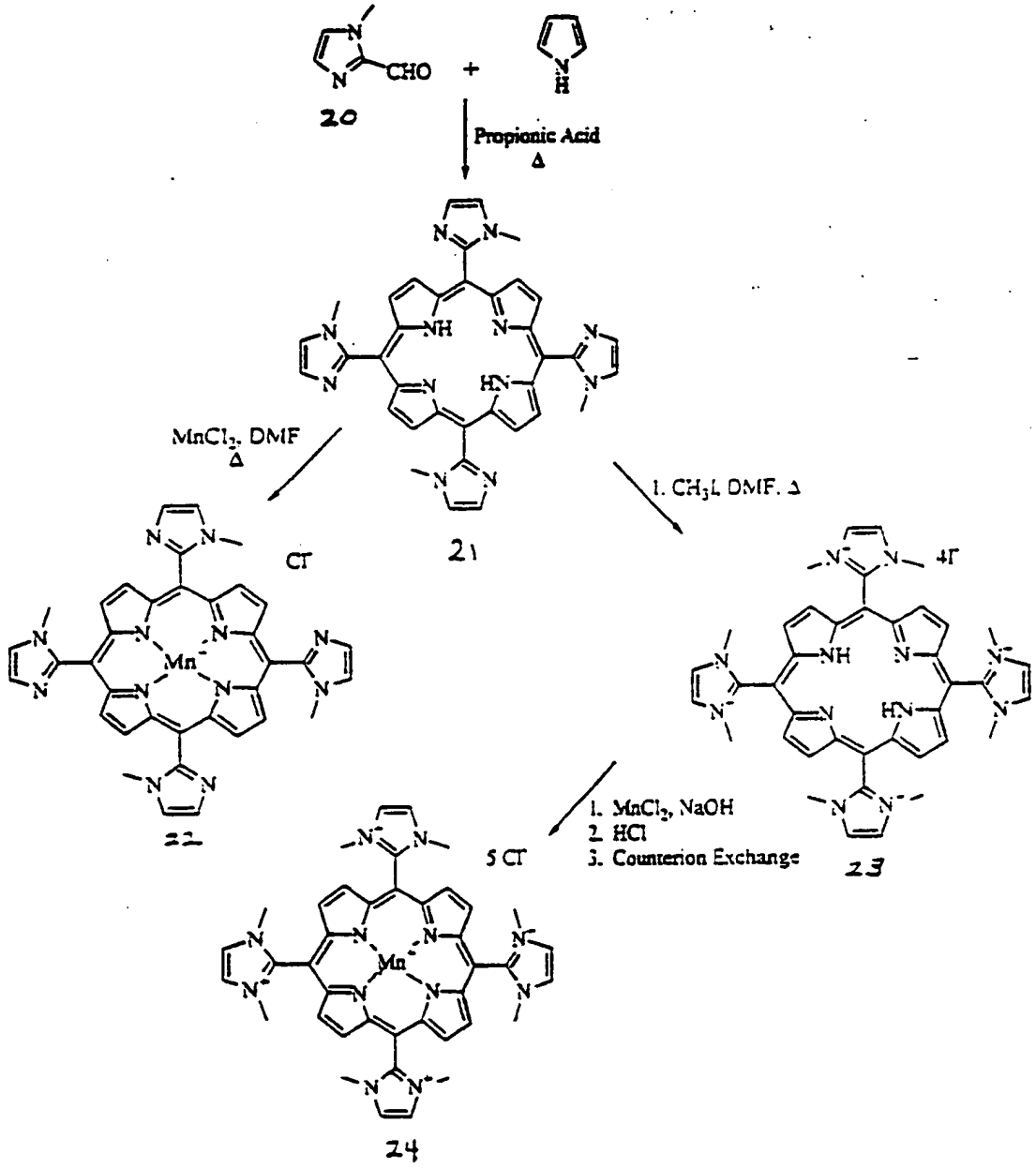
A solution of porphyrin **17** (140 mg, 0.29 mmol), CH_3I (4 mL), and DMF (20 mL) in a sealed tube was heated at 100 °C for 48 h. The precipitate that formed during the reaction was filtered and washed with ether. Purification of the solid precipitate by the double precipitation method provided porphyrin **18** (120 mg, 71%) as a purple solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ -3.4 (s, 2 H), 4.09, 4.06 (2 s, 6 H, atropisomer N-CH_3), 9.07 (d, 2 H), 9.2 (d, 2 H), 9.4 (d, 4 H), 9.9 (d, 4 H), 10.96 (s, 2 H).

3. [5,15-Bis(3-methylthiazolium-2-yl)porphyrinato]manganese(III) Trichloride (19).

Porphyrin **18** (120 mg, 0.21mmol) was dissolved in water (25 mL) and the solution pH was adjusted to pH = 12 by dropwise addition of 6N NaOH. Solid $MnCl_2$ (147

mg) was added (the resulting pH = 8.7) and the reaction mixture was stirred for 30-60 min. The reaction mixture was filtered through a fritted funnel lined with a filter paper. The pH of the filtrate was adjusted to pH = 4-5 (1N HCl) and the solution was filtered. The filtrate was subjected to the double precipitation method to provide a mixture of porphyrins 18 and 19. The resulting mixture was separated by column chromatography (9:0.5:0.5 CH_3CN/water/saturated KNO_3) to provide porphyrin 19 (25 mg, 18%) as a dark solid: mp >300 °C; UV-vis λ_{max} = 450.5 nm, ε = 5.99 x 10^4 L/cm-mol.

VI. [5,10,15,20-Tetrakis(1-methylimidazol-2-yl)porphyrinato]manganese(III) Chloride (22) and [5,10,15,20-Tetrakis(1,3-dimethylimidazolium-2-yl)-porphyrinato]manganese(III) Pentachloride (24)



1. 5,10,15,20-Tetrakis(1-methylimidazol-2-yl)porphyrin (21).

In a foil-covered 1-L three-neck flask equipped with magnetic stirrer, thermometer, and condenser was placed aldehyde **20** (2.0 g, 18.2 mmol) and propionic acid (400 mL). The reaction mixture was heated to 120 °C at which time pyrrole (1.26 mL, 18.2 mmol) was added. The reaction mixture was heated under reflux for an additional 4.5 h and was stirred at room temperature for 3 d. The propionic acid was removed *in vacuo*, the dark residue was dissolved in a solution of 5% $MeOH/CH_2Cl_2$ and adsorbed onto silica gel (18 g). Repeated column chromatographic purification provided porphyrin 21 (280 mg, 10%) as a purple solid: ^1H NMR (300 MHz, $CDCl_3$) δ -2.94, -2.90, -2.84 (3 s, 2 H, atropisomer NH), 3.39-3.58 (multiple s, 12 H, atropisomer N-CH_3), 7.50 (d, 4 H), 7.71 (d, 4 H), 8.92 (m, 8 H).

2. [5,10,15,20-Tetrakis(1-methylimidazol-2-yl)porphyrinato]manganese(III) Chloride (22).

A solution of porphyrin 21 (29.9 mg, 0.047 mmol) and $MnCl_2$ (61 mg, 0.48 mmol) in DMF (12 mL) was heated at 120 °C for 14 h. The mixture was cooled to room temperature while exposed to a stream of air, and concentrated by rotary evaporation. Purification by column chromatography ($CHCl_3$/MeOH/concentrated NH_4OH/EtOAc) provided porphyrin 22 (12.5 mg, 37%) as a black solid: mp >300°C; UV-vis λ_{max} = 463.0 nm; ε = 9.35 x 10^4 L/cm-mol; API MS *m/z* = 683 $[C_{36}H_{28}MnN_{12}]^+$.

3. 5,10,15,20-Tetrakis(1,3-dimethylimidazolium-2-yl)porphyrin Tetrachloride (23).

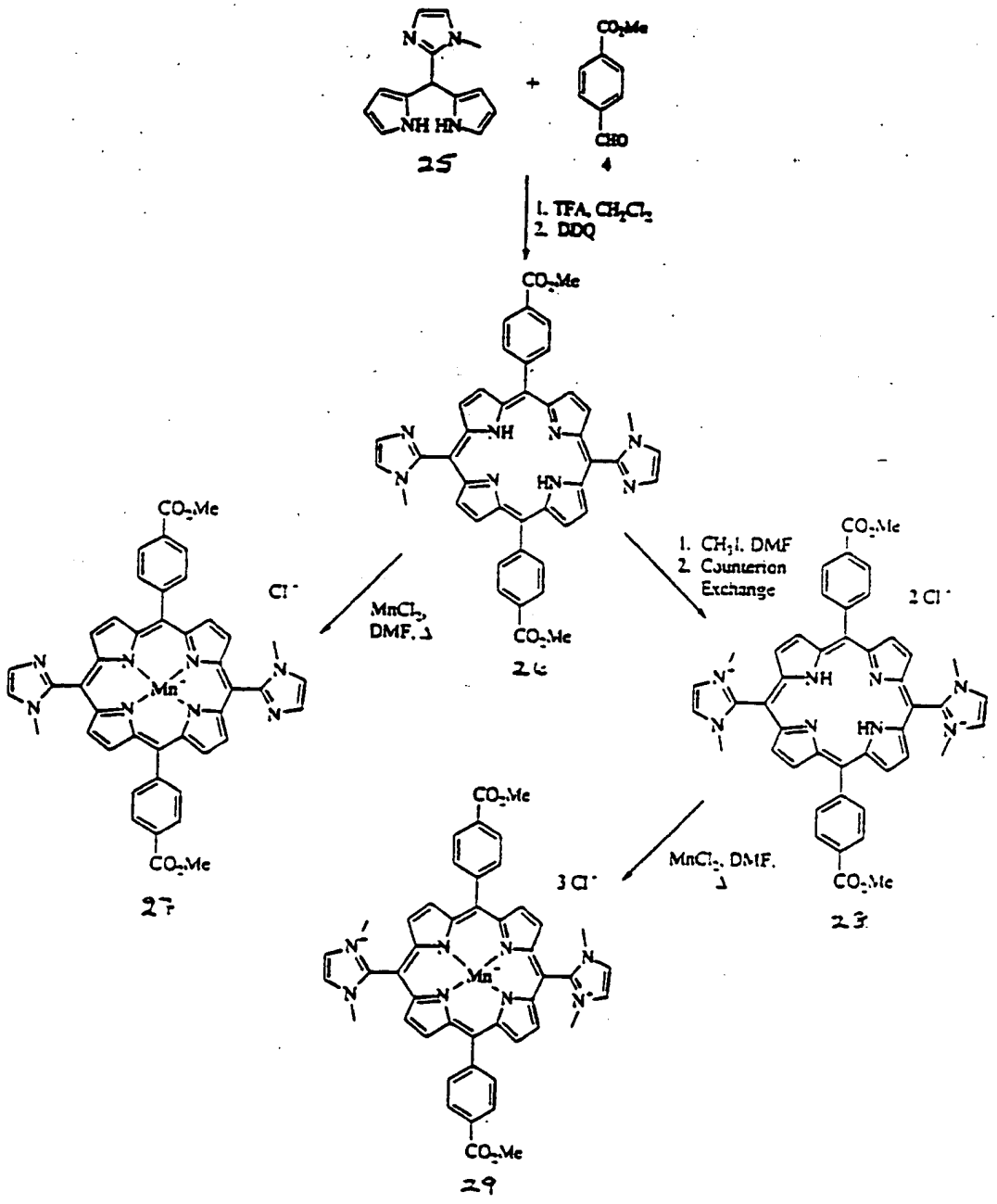
A solution of porphyrin 21 (589 mg, 0.934 mmol) and CH_3I (3 mL, 48 mmol) in DMF (10 mL) was heated in a sealed tube at 100 °C for 14 h. The reaction mixture

was poured into ethyl acetate (200 mL) causing porphyrin 23 to precipitate as the iodide salt. The solution was filtered and the brown solid was washed with EtOAc and ether. The product was purified by column chromatography (CH_3CN/water/saturated KNO_3) and subjected to the double precipitation method to provide porphyrin 23 (540 mg, 69%) as a purple solid: ^1H NMR (300 MHz, DMSO-d_6) δ -3.22 (s, 2 H), 3.78 (s, 24 H), 8.60 (s, 8 H), 9.44 (s, 8 H).

4. [5,10,15,20-Tetrakis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Pentachloride (24).

Porphyrin 23 (1.0 g, 0.83 mmol) was dissolved in MeOH (550 mL) then $MnCl_2$ (1.57 g, 12.5 mmol) was added. The solution pH was adjusted to pH = 7.3 with 6N NaOH while bubbling a stream of air into the reaction mixture. The pH of the solution was maintained pH > 7.3 for 1 h then adjusted to pH = 4.5 with 1N HCl. The solution was filtered and the precipitate subjected to the double precipitation method and dried to provide porphyrin 24 (0.570 g, 74%) as a solid: mp >300 °C; UV-vis λ_{max} = 460.5 nm; ε = 8.38 x 10^4 L/cm-mol: FAB MS *m/z* = 778 $[C_{40}H_{40}MnN_{12}]^{+}$.

VII. [5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1-methylimidazol-2-yl)-porphyrinato]manganese(III) Chloride (27) and [5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Trichloride (29).


25
4
1. TFA, CH2Cl2
2. DDQ
26
MnCl2, DMF, Δ
1. CH3I, DMF
2. Counterion Exchange
27
23
MnCl2, DMF, Δ
29

1. 5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1-methylimidazol-2-yl)p rphyrin (26).

In a foil-covered 500-mL three-necked flask, equipped with a magnetic stirrer and N_2 inlet, was placed dipyrromethane 25 (0.71 g, 3.09 mmol), CH_2Cl_2 (310 mL), aldehyde 4 (50 mg, 3.09 mmol), and NaCl (22.4 mg, 0.35 mmol). The reaction mixture was stirred for 10 min, then TFA (1.48 mL, 19.2 mmol) was added. After a stirring period of 4 h at room temperature, DDQ (1.05 g, 4.65 mmol) was added. The reaction mixture was stirred overnight and the solvent was removed *in vacuo*. The residue was adsorbed onto silica gel (10 g) then purified by column chromatography (gradient elution 2-4% EtOAc/hexanes) to provide porphyrin 26 (220 g, 24%) as a purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ -2.85 (s, 2 H), 3.43, 3.49 (2 s, 6 H, atropisomer N-CH_3), 4.14 (s, 6 H), 7.49 (d, 2 H), 7.68 (d, 2 H), 8.30 (d, 4 H), 8.48 (d, 4 H), 8.87 (m, 8 H).

2. [5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1-methylimidazol-2-yl)-porphyrinato]manganese(III) Chloride (27).

A solution of porphyrin 26 (50.7 mg, 0.071 mmol) and $MnCl_2$ (88.6 mg, 0.70 mmol) in DMF (20 mL) was heated at 120 °C for 14 h. The mixture was cooled to room temperature while exposed to a stream of air, then concentrated by rotary evaporation. Purification by column chromatography (gradient elution 5-10% MeOH/CH_2Cl_2) provided porphyrin 27 (25 mg, 42%) as a black solid: mp >300 °C; UV-vis λ_{max} = 463.0 nm; ε = 6.70 x 10^4 L/cm-mol; FAB MS *m/z* = 791 $[C_{44}H_{32}MnN_8O_4]^+$.

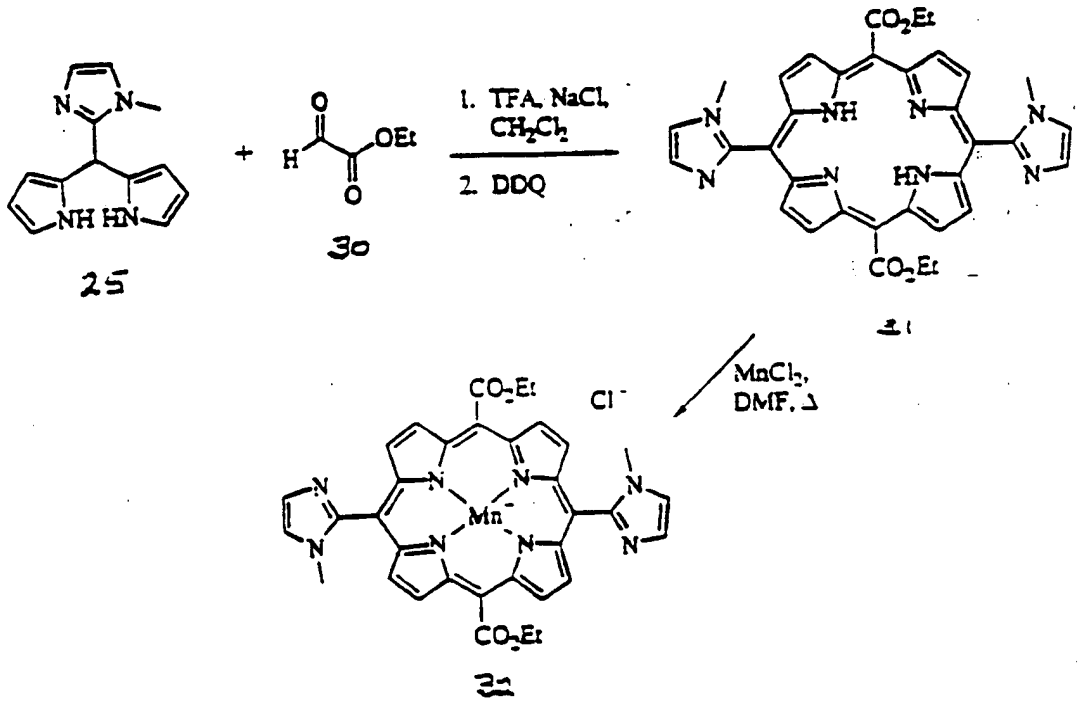
3. 5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1,3-dimethylimidazolium-2-yl)-porphyrin Dichloride (28).

A solution of porphyrin **26** (80 mg, 0.11 mmol), DMF (7 mL) and CH_3I (0.150 mL) was stirred at room temperature for 4 h. The solvent was removed by rotary evaporation to give a dark colored residue. The residue was purified by column chromatography ($CHCl_3$/MeOH/concentrated NH_4OH/EtOAc) to provide porphyrin **28** (21 mg, 18%) as a purple solid: ^1H NMR (300 MHz, DMSO-d_6) δ -3.02 (s, 2 H), 3.73 (s, 12 H), 4.08 (s, 6 H), 8.45 (q, 8 H), 8.56 (s, 4 H), 9.13 (s, 8 H); API MS *m/z* = 384 $[C_{46}H_{40}MnN_8O_4]^{+2}$.

4. [5,15-Bis(4-carbomethoxyphenyl)-10,20-bis(1,3-dimethylimidazolium-2-yl)-porphyrinato]manganese(III) Trichloride (29).

A solution of porphyrin **28** (19.5 mg, 0.022 mmol) and $MnCl_2$ (22.4 mg, 0.18 mmol) in DMF (5 mL) was heated at 120 °C for 14 h. The reaction mixture was cooled to room temperature while exposed to a stream of air, then concentrated by rotary evaporation. Purification by column chromatography ($CHCl_3$/MeOH/concentrated NH_4OH/EtOAc) provided crude porphyrin **28**. Purification by the double precipitation method and drying provided porphyrin **29** (6.5 mg, 37%) as a solid: mp >300 °C; UV-vis λ_{max} = 447.5 nm; ε = 1.27 x 10^5 L/cm-mol; FAB MS *m/z* = 856 $[C_{46}H_{38}MnN_8O_4]^{+2}$.

VIII. [5,15-Bis(carboethoxy)-10,20-bis(1-methylimidazol-2-yl)porphyrinato]-manganese(III) Chloride (32).



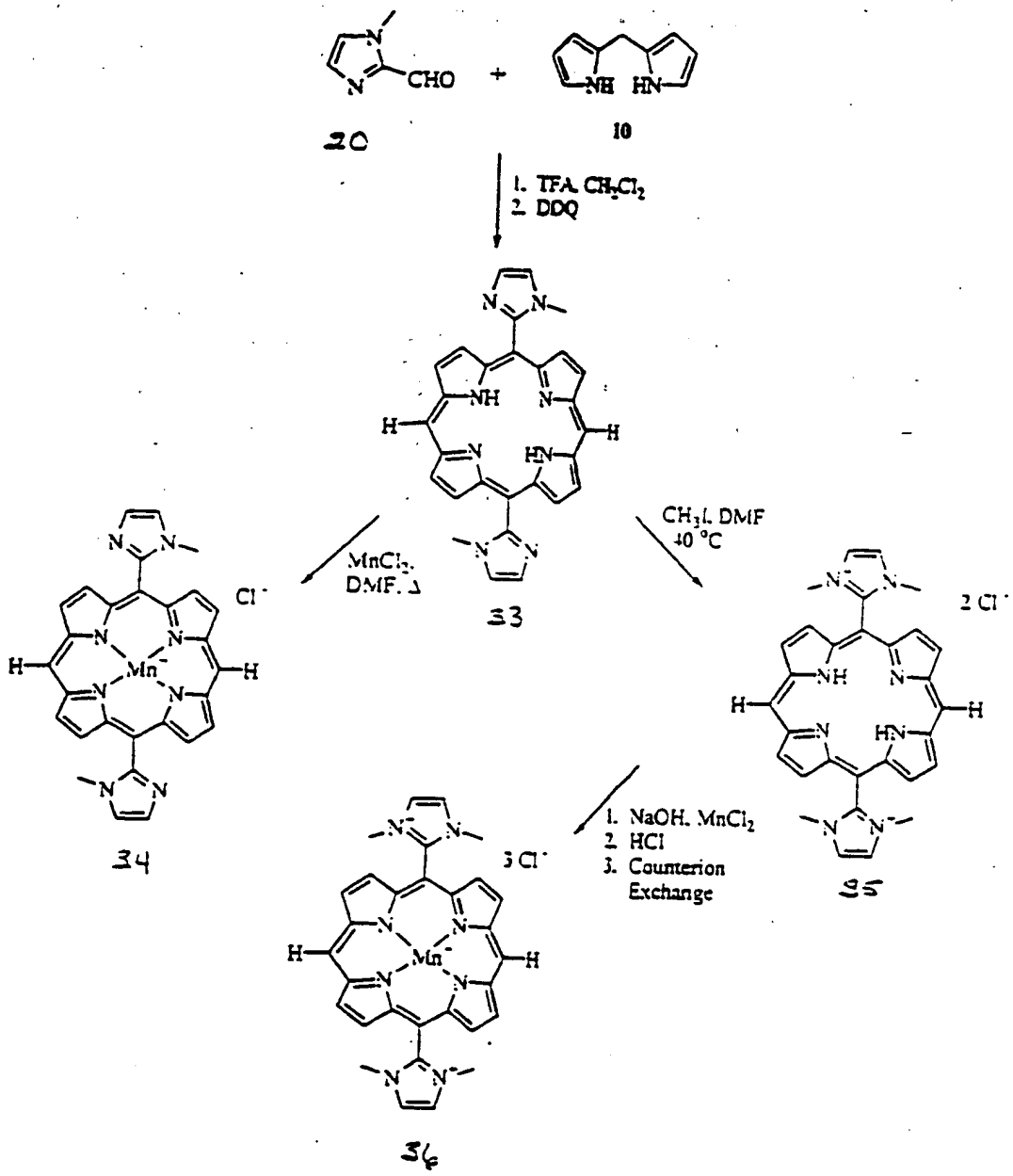
1. 5,15-Bis(carboethoxy)-10,20-bis(1-methylimidazol-2-yl)porphyrin (31). In a foil-covered 500-mL three-necked flask, equipped with a magnetic stirrer and N_2 inlet, was placed dipyrromethane **25** (0.5 g, 2.2 mmol), CH_2Cl_2 (220 mL), and aldehyde **30** (225 mg, 2.2 mmol). The reaction mixture was stirred for 10 min, then TFA (1.0 mL, 12.9 mmol) was added. After a stirring period of 2 h at room temperature, DDQ (750 mg, 3.3 mmol) was added, and the reaction mixture was stirred overnight. Triethylamine (2.0 mL) was added, the solvent was evaporated *in vacuo*, and the residue adsorbed onto silica gel (10 g). Purification by column chromatography (5% EtOH/$CHCl_3$) provided porphyrin **31** (86 mg, 13%) as a

purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ -3.08, -3.06 (2 s, 2 H, atropisomer NH), 1.82 (t, 6 H), 3.40, 3.49 (2 s, 6 H, atropisomer N-CH_3), 5.11 (q, 4 H), 7.53 (d, 2 H), 7.72 (d, 2 H), 8.94 (m, 4 H), 9.50 (d, 4 H).

2. [5,15-Bis(carboethoxy)-10,20-bis(1-methylimidazol-2-yl)porphyrinato]-manganese(III) Chloride (32).

A solution of porphyrin 31 (27.7 mg, 0.045 mmol) and $MnCl_2$ (59.1 mg, 0.47 mmol) in DMF (12.5 mL) was heated at 120 °C for 14 h. Additional $MnCl_2$ (29 mg, 0.23 mmol) was added and the reaction mixture was heated for another 2 h. The reaction mixture was cooled to room temperature while exposed to a stream of air, then concentrated by rotary evaporation. Air was bubbled into a solution of the product dissolved in ethanol with two drops of 1N HCl. The solvent was evaporated *in vacuo* to give a dark colored residue. Purification by column chromatography (gradient elution 10-30% EtOH/$CHCl_3$) provided porphyrin 32 (6.5 mg, 35%) as a black solid: mp >300 °C; UV-vis λ_{max} = 458.5 nm; ε = 6.01 x 10^4 L/cm-mol; API MS *m/z* = 667 $[C_{34}H_{28}MnN_8O_4]^+$.

IX. [5,15-Bis(1-methylimidazol-2-yl)porphyrinato]manganese(III) Chloride (34) and [5,15-Bis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Trichloride (36).


CHO
+
NH HN
20
10
1. TFA, CH_2Cl_2
2. DDQ
NH
N
HN
H
33
$MnCl_2$,
DMF, Δ
CH_3I, DMF
40 °C
Cl⁻
Mn
34
2 Cl⁻
35
1. NaOH, $MnCl_2$
2. HCl
3. Counterion
Exchange
3 Cl⁻
36

1. 5,15-Bis(1-methylimidaz l-2-yl)porphyrin (33).

In a foil-covered l-L three-necked flask, equipped with a magnetic stirrer and N_2 inlet, was placed dipyrromethane **10** (1.0 g, 6.84 mmol), CH_2Cl_2 (680 mL), and aldehyde **20** (753 mg, 6.84 mmol). The reaction mixture was stirred for 10 min, then TFA (3.1 mL, 40.2 mmol) was added. After a stirring period of 2 h at room temperature, DDQ (2.3 g, 10.1 mmol) was added and the reaction mixture was stirred overnight. Triethylamine (5.75 mL) was added into the reaction mixture, the solvent was evaporated *in vacuo* and the residue was adsorbed onto silica gel (15 g). Purification by column chromatography (6% MeOH/CH_2Cl_2) provided porphyrin **33** (0.120 g, 7%) as a purple solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ -3.28 (s, 2 H), 3.45, 3.52 (2 s, 6 H, atropisomer N-CH_3), 7.53 (d, 2 H), 7.74 (d, 2 H), 9.07 (m, 4 H), 9.46 (d, 4 H), 10.37 (s, 2 H).

2. [5,15-Bis(1-methylimidazol-2-yl)porphyrinato]manganese(III) Chloride (34).

A solution of porphyrin **33** (50 mg, 0.106 mmol) and $MnCl_2$ (180 mg, 1.4 mmol) in DMF (20 mL) was heated at 120 °C for 14 h. The mixture was cooled to room temperature while exposed to a stream of air, then concentrated by rotary evaporation. Purification by column chromatography (33% MeOH/$CHCl_3$) provided porphyrin **34** (32 mg, 53%) as a black solid: mp >300 °C; UV-vis λ_{max} = 454.5 nm; ε = 4.98 x 10^4 L/cm-mol; API MS *m/z* = 523 $[C_{28}H_{20}MnN_8]^+$.

3. 5,15-Bis(1,3-dimethylimidazolium-2-yl)porphyrin Dichloride (35).

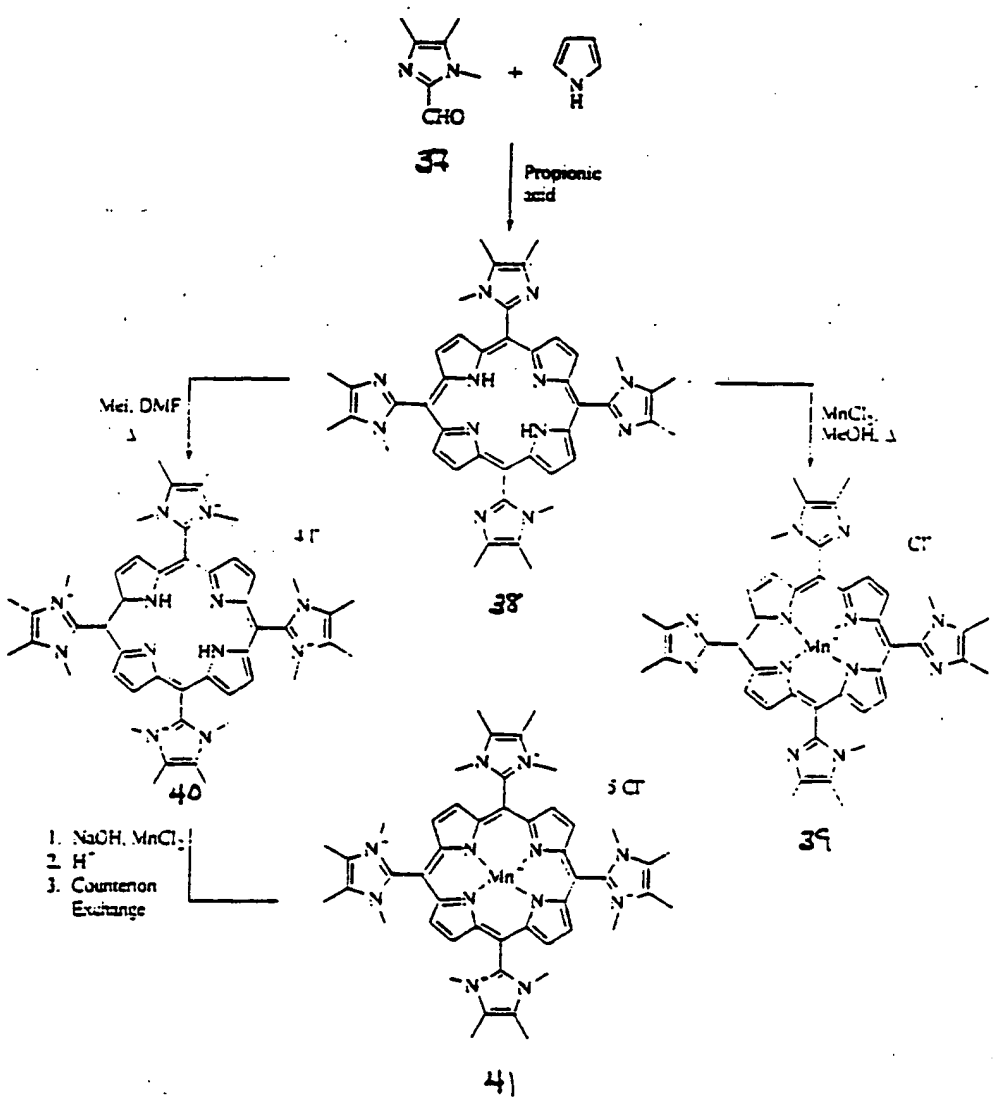
Porphyrin **33** (95 mg, 0.20 mmol) was dissolved in DMF (15 mL), CH_3I (0.5 mL, 8.03 mmol) was added, and the reaction mixture stirred for 48 h. The DMF was evaporated *in vacuo* and the dark colored residue was purified by column chromatography (gradient elution 30% MeOH/CH_2Cl_2 to 6:4:1 $CHCl_3$/MeOH/1N

HCl) to provide porphyrin 35 (150 mg, 99%) as a purple solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ -3.54 (s, 2 H), 3.79 (s, 12 H), 8.55 (s 4 H), 9.28 (d, 4 H), 11.00 (s, 2 H).

4. [5,15-Bis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Trichloride (36).

Porphyrin 35 (150 mg, 0.198 mmol) was dissolved in water (50 mL) and the solution pH was adjusted to pH = 12 with 6N NaOH. Manganese chloride (375 mg, 2.98 mmol) was added and the reaction mixture was stirred for 30 min. The solution was filtered on a fine fritted filter funnel, the pH of the filtrate was adjusted to pH = 4 (1N HCl) and the solution was filtered. Purification of the solid filter cake by the double precipitation method and drying provided porphyrin 36 (25.5 mg, 20%) as a solid: mp >300 °C; UV-vis λ_{max} = 447.5 nm; ε = 8.66 x 10^4 L/cm-mol; API MS *m/z* = 554 $[C_{30}H_{28}MnN_8-H]^+$.

X. [5,10,15,20-Tetrakis(1,4,5-trimethylimidazol-2-yl)porphyrinato]-manganese(III)Chloride (39) and [5,10,15,20-Tetrakis(1,3,4,5-tetramethyl-imidazolium-2-yl)porphyrinato]manganese(III)Pentachloride (41).


CHO
37
Propionic acid
MeI, DMF
Δ
MnCl2
MeOH, Δ
38
4 I⁻
40
39
5 Cl⁻
1. NaOH, MnCl2
2. H+
3. Counterion Exchange
41

1. [5,10,15,20-Tetrakis(1,4,5-trimethylimidazol-2-yl)porphyrin (38).

1,4,5-Trimethylimidazole-2-carboxaldehyde (37, 750mg, 5.42 mmol), prepared according to literature procedure (Alcalde, E. et al, Tetrahedron 52:15171-15188 (1996)), was dissolved in propionic acid (120 mL) in a 250 mL three neck round-bottom flask equipped with a thermometer and a condenser. The solution was heated to reflux then pyrrole (0.38 mL, 5.42 mmol) was added. The reaction mixture was heated at reflux for an additional 5 h, then cooled to room temperature while exposed to air overnight. The propionic acid was removed by vacuum distillation yielding a dark solid residue which was adsorbed onto silica gel. Purification by column chromatography (gradient elution 5-10% MeOH:CH_2Cl_2) provided porphyrin 38 as a mixture of atropisomers (108 mg, 10.7%). ^1H NMR (300 MHz, $CDCl_3$)δ-2.90, -2.85, -2.78 (3 s, 2H, atropisomer NH), 2.50 (s, 12 H), 2.57 (s, 12 H), 3.15-3.42 (multiple s, 12 H, atropisomer N-CH_3), 8.91 (multiple s, 8 H, atropisomer).

2. [5,10,15,20-Tetrakis(1,4,5-trimethylimidazol-2-yl)porphyrinato]manganese(III) Chloride (39).

Porphyrin 38 (40 mg, 0.05 mmol) was dissolved in MeOH (7 mL) in a 25 mL round-bottom flask equipped with a condenser. Manganese(II) chloride (101 mg, 0.81 mmol) was added and the reaction mixture was heated under reflux for 2 h. Air was bubbled into the reaction mixture for 20 min then methanol was evaporated *in vacuo*. Purification of the residue by column chromatography provided porphyrin 39 as a black solid (12 mg, 27%): mp>300°C; UV-vis λ_{max}=474.5 nm, ϵ=9.74x10^{4}L/cm-mol; API MS *m/z*=795[$C_{44}H_{44}MnN_{12}$]$^+$.

3. [5,10,15,20-Tetrakis(1,3,4,5-tetramethylimidazolium-2-yl)porphyrin Tetraiodide (40).

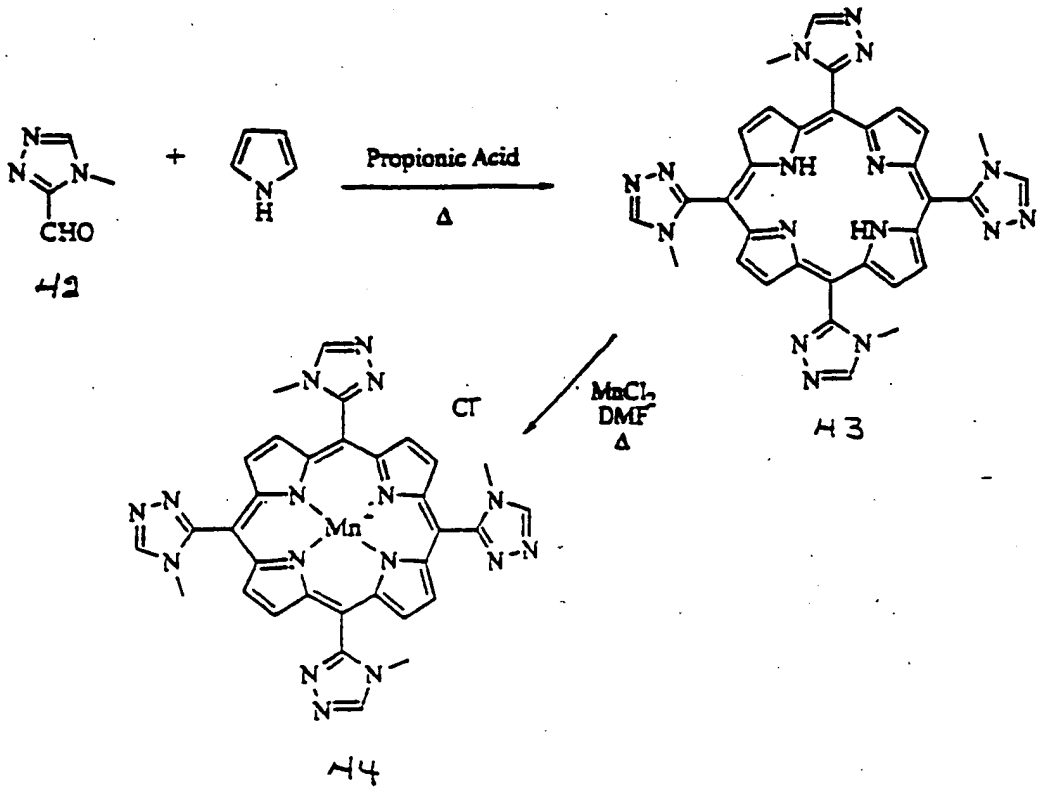
Porphyrin 38 (40 mg, 0.05 mmol) was dissolved in DMF (5 mL) in a sealed tube reactor. Methyl iodide (1 mL, 16 mmol) was added and the sealed tube heated at

60°C overnight. Dilution of the reaction mixture with EtOAc (100 mL) resulted in the precipitation of crude product **40** which was collected by vacuum filtration then purified by column chromatography to provide porphyrin **40** as a dark purple solid (25 mg, 35%): ^{1}H NMR (300 MHz, DMSO-*d6*)δ-3.20 (s, 2 H), 2.72 (s, 24 H), 3.58 (s, 24 H), 9.40 (s, 8 H).

4. [5,10,15,20-Tetrakis(1,3,4,5-tetramethylimidazolium-2-yl)porphyrinato]-manganese(III) Pentachloride (41).

Porphyrin **40** (25 mg, 0.02 mmol) was dissolved in methanol (7 mL) in a round-bottomed flask (25 mL). Manganese(II) chloride (50 mg, 0.4 mmol) was added and the reaction mixture was heated at 60°C for 6 h. NaOH (2N, 2 drops) was added and the reaction mixture stirred for an additional hour. The reaction mixture was filtered through celite and washed through with MeOH. Analysis of the filtrate by UV-vis spectroscopy indicated that the reaction was incomplete. The solvent was evaporated off and the residue redissolved in MeOH (7 mL), then $MnCl_2$ (50 mg, 0.4 mmol) was added and the reaction mixture was heated at 60°C for 3 h. Air was bubbled into the reaction mixture for 20 min. The reaction mixture was filtered over celite and washed with MeOH. Evaporation of the solvents *in vacuo* provided a brown residue. Purification of the product by the double precipitation method provided porphyrin **41** (10 mg, 51%) as a brown solid: mp>300°C; UV-vis λ_{max}=451.5 nm, ϵ=9.29x10^4 L/cm-mol.

XI. [5,10,15,20-Tetrakis(4-methyl-1,2,4-triazol-3-yl)porphyrinato]manganese(III) Chloride (44).


Propionic Acid
Δ
CHO
42
43
MnCl2
DMF
Δ
CT
Mn
44

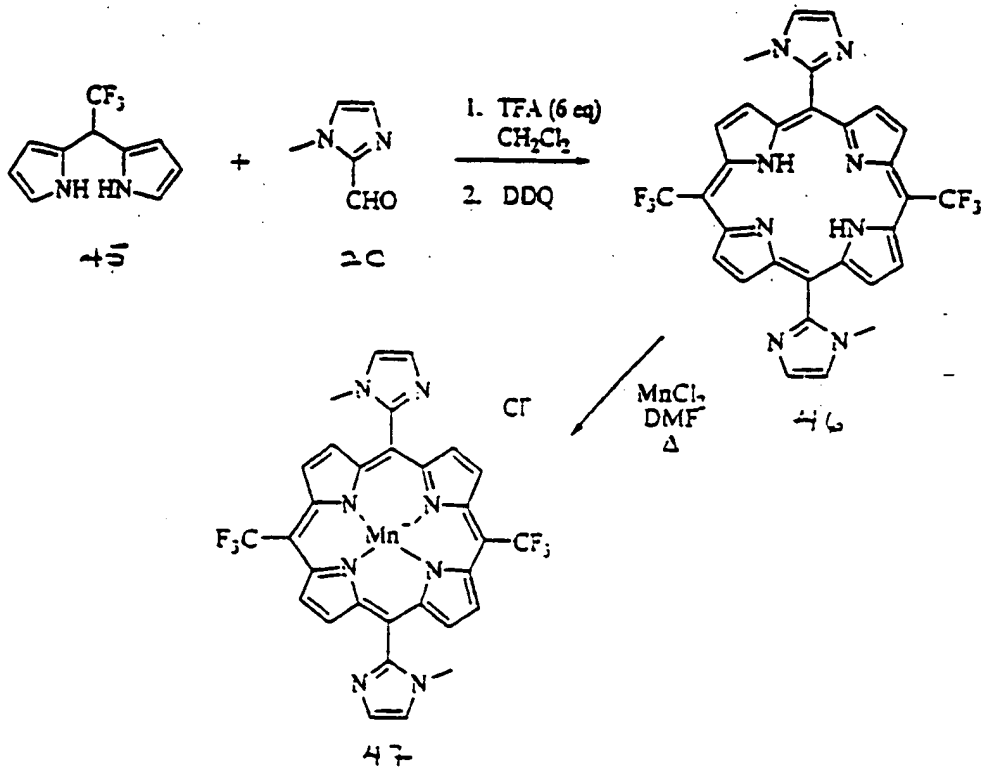
1. 5,10,15,20-Tetrakis(4-methyl-1,2,4-triazol-3-yl)porphyrin (43).

4-Methyl-1,2,4-triazole-3-carboxaldehyde (42, 1.06 g, 9.5 mmol), prepared according to literature procedure (Moderhack, D.; Hoppe-Tichy, T. *J. Prakt. Chem/Chem-Ztg.* 1996, *338(2)*, 169-171), was dissolved in propionic acid (180 mL) in a 250-mL three-neck round bottom flask covered with foil and equipped with a condenser. The solution was heated to reflux, and then pyrrole (0.66 mL, 9.5 mmol) was added. The reaction mixture was stirred at reflux for an additional 2.5 h. The reaction was then cooled to room temperature while exposed to air over 2 days. Evaporation of the propionic acid under reduced pressure provided a dark residue which was adsorbed onto silica gel. Repeated purification by column chromatography (gradient elution, $CHCl_3$, MeOH, concentrated NH_4OH, EtOAc) provided porphyrin 43 (219 mg, 14.6%) as a solid mixture of atropiosomers: ^1H NMR (300 MHz, DMSO-d_6) δ -3.36, -3.13, -3.09 (3 s, 2 H, atropisomer NH), 3.43-3.64 (multiple s, 12 H, atropisomer N-CH_3), 9.03 (broad s, 8 H), 9.20 (s, 4 H).

2. [5,10,15,20-Tetrakis(4-methyl-1,2,4-triazol-3-yl)porphyrinato]manganese(III) Chloride (44).

Porphyrin 43 (77 mg, 0.12 mmol) was dissolved in DMF (30 mL) in a 100-mL round bottom flask equipped with a condenser. Manganese (II) chloride (156 mg, 1.24 mmol) was added and the reaction was heated at 130 °C overnight. The reaction mixture was exposed to a stream of air as it cooled to room temperature. The porphyrin precipitated out upon the addition of CH_2Cl_2 (5-10 mL). The solids were filtered and washed with EtOH and CH_2Cl_2 to provide porphyrin 44 (45 mg, 51%) as a brown solid: mp >300 °C; UV-vis λ_{max} = 452.5 nm; ε = 8.10 x 10^4 L/ cm-mol; FAB-MS *m/z* = 787 $[C_{32}H_{24}MnN_{16}]^+$.

XII. [5,15-Bis(trifluoromethyl)-10,20-bis(imidazol-2-yl)porphyrinato]-manganese(III) Chloride (47).



1. 5,15-Bis(trifluoromethyl)-10,20-bis(imidazol-2-yl)porphyrin (46).

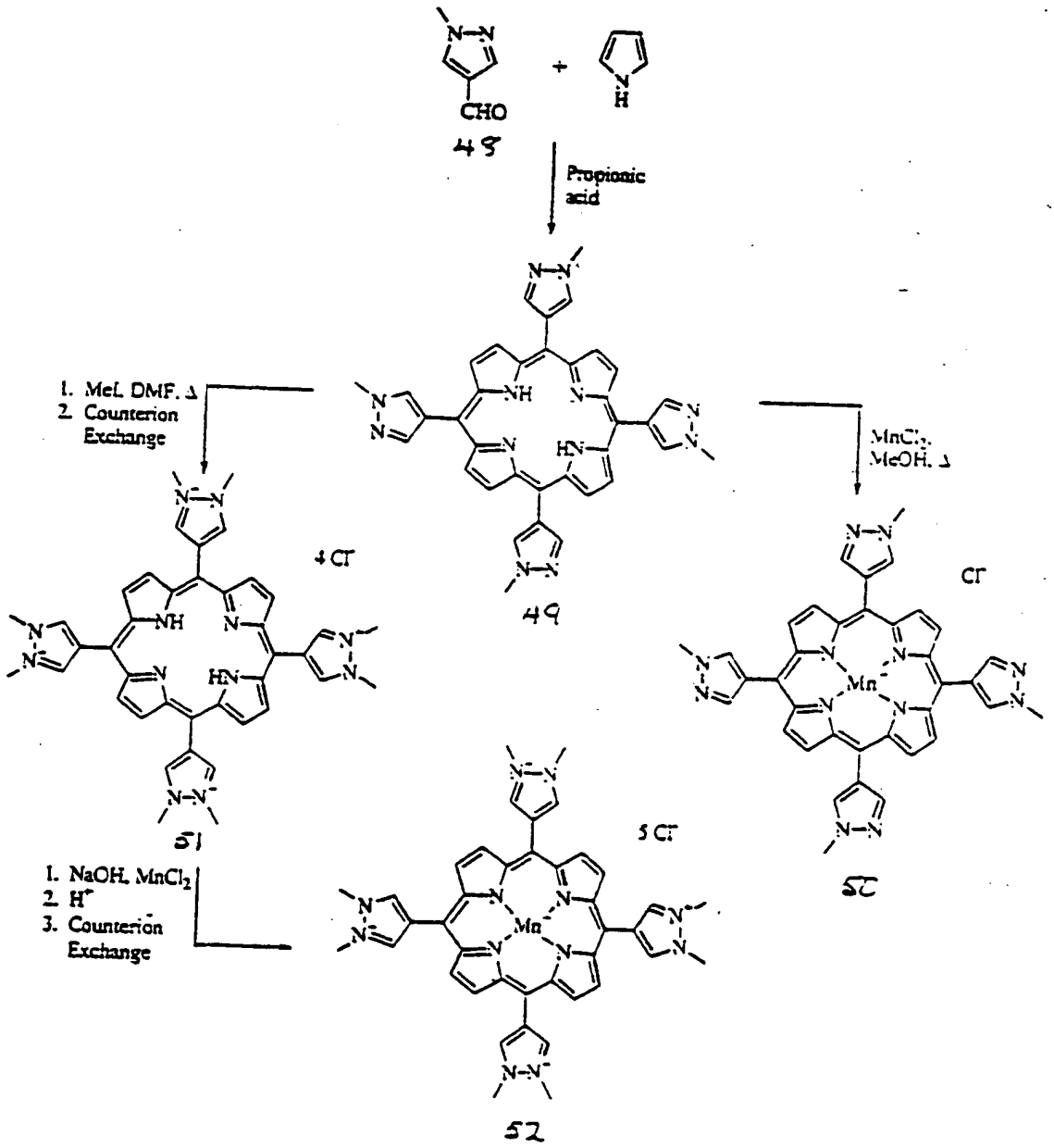
In a foil-covered 1-L three-neck round bottom flask, equipped with a magnetic stirrer and a N_2 outlet, was added dipyrromethane 45 (1.13 g, 5.28 mmol), 1-methylimidazole-2-carboxaldehyde (20, 582 mg, 5.28 mmol), sodium chloride (32 mg, 0.54 mmol) and CH_2Cl_2 (530 mL). The reaction mixture was stirred for 10 min, then TFA (2.40 mL, 31.1 mmol) was added. After a stirring period of 105 min, DDQ (1.81 g, 7.97 mmol) was added, and the mixture was stirred overnight. The solvent was removed by rotary evaporation, and the crude residue was adsorbed onto silica gel (3 g). Purification by column chromatography (gradient elution, 5-10% MeOH/CH_2Cl_2) provided porphyrin 46 (455 mg, 34%) as a black solid: ^1H

NMR (300 MHz, $CDCl_3$) δ -2.87 (s, 2 H), 3.56 (m, 6 H), 7.85 (d, 2 H), 8.05 (d, 2 H), 8.99 (m, 4 H), 9.81 (m, 4 H); API-MS *m/z* = 607 $[C_{30}H_{20}F_6N_8 + H]^+$.

2. [5,15-Bis(trifluoromethyl)-10,20-bis(imidazol-2-yl)porphyrinato]manganese(III) Chloride (47).

A solution of free porphyrin **46** (113 mg, 0.186 mmol) and $MnCl_2$ (360 mg, 2.86 mmol) in DMF (15 mL) was warmed to 120 °C for 6 h. The mixture was cooled to room temperature while exposed to a stream of air, then concentrated by rotary evaporation. The crude residue was dissolved in 10% MeOH/CH_2Cl_2 (100 mL), then adsorbed onto silica gel (1 g). Purification by column chromatography (10% MeOH/CH_2Cl_2) provided porphyrin **47** (45 mg, 35%) as a dark green solid: mp >300 °C; UV-vis λ_{max} = 456.5 nm; ε = 1.98 x 10^4 L/ cm-mol; API-MS *m/z* = 659 $[C_{30}H_{18}F_6MnN_8]^+$.

XIII. [5,10,15,20-Tetrakis(1-methylpyrazol-4-yl)porphyrinato]manganese(III) Chloride (50) and [5,10,15,20-Tetrakis(1,2-dimethylpyrazolium-4-yl)porphyrinato]-manganese(III) Pentachloride (52).



1. 5,10,15,20-Tetrakis(1-methylpyrazol-4-yl)porphyrin (49).

To a refluxing solution of propionic acid (200 mL) and 1-methylpyrazole-4-carboxaldehyde (48, 0.92 g, 8.32 mmol), prepared according to literature procedure (Finar, I. L.; Lord, G. H. *J. Chem. Soc.* 1957, 3314-3315), was added pyrrole (0.63 mL, 8.32 mmol). The reaction was covered with foil and was heated under reflux for 3.5 h. Upon cooling the reaction mixture was exposed to air overnight. The propionic acid was then removed by vacuum distillation. The crude residue was dissolved in 5% MeOH/CH_2Cl_2, then adsorbed onto silica gel (5.3 g). Purification by column chromatography (5% MeOH/CH_2Cl_2) provided porphyrin 49 as a purple solid (231 mg, 17.5%): ^{1}H NMR (300 MHz, DMSO-d_6) δ -2.74 (s, 2 H), 4.28 (s, 12 H), 8.31 (s, 4 H), 8.67 (s, 4 H), 9.16 (s, 8 H).

2. [5,10,15,20-Tetrakis(1-methylpyrazol-4-yl)porphyrinato]manganese(III) Chloride (50).

Porphyrin 49 (50 mg, 7.93 x 10^{-2} mmol) was dissolved in DMF (10 mL) in a 25-mL round bottom flask equipped with a condenser. Manganese (II) chloride (150 mg, 1.19 mmol) was added and the reaction was heated at 125 °C for 4 h. A stream of air was introduced and the reaction heated for an additional 2 h. The reaction was diluted with EtOAc (100 mL) and the crude product was collected by vacuum filtration. Purification of the residue by column chromatography (10% MeOH/CH_2Cl_2) followed by counterion exchange provided porphryin 50 as a green solid (15 mg, 25%): mp >300 °C; UV-vis λ_{max} = 471.0 nm, ε = 9.55 x 10^4 L/cm-mol; API MS *m/z* = 683 $[C_{36}H_{28}MnN_{12}]^+$.

3. 5,10,15,20-Tetrakis(1,2-dimethylpyrazolium-4-yl)porphyrin Tetrachloride (51).

Porphyrin 49 (200 mg, 0.32 mmol) was dissolved in DMF (15 mL) in a sealed tube reactor. Methyl iodide (2 mL, 32 mmol) was added and the sealed tube heated at

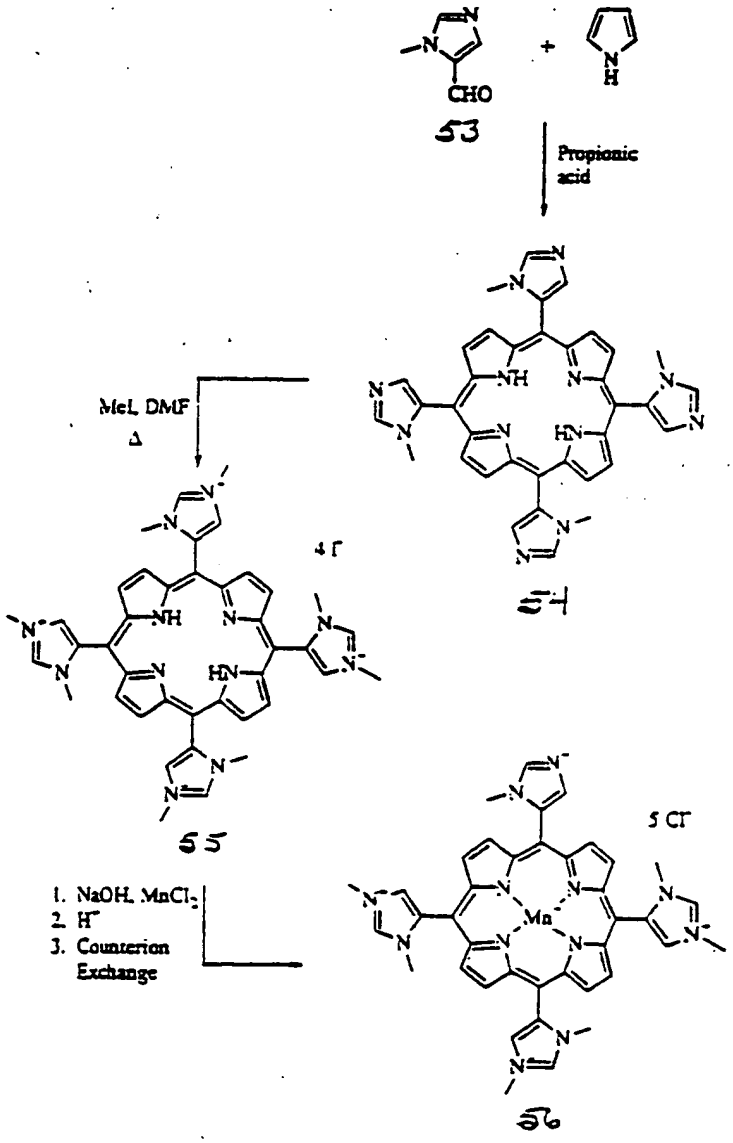
125 °C for 6 h. Dilution of the reaction mixture with EtOAc resulted in the precipitation of crude product which was collected by vacuum filtration and initially purified by column chromatography (8:1:1 CH_3CN/water/saturated KNO_3). Further purification by the double precipitation method provided porphyrin 51 as a dark purple solid (45 mg, 17%): ^1H NMR (300 MHz, DMSO-d_6) δ -3.16 (s, 2 H), 4.55 (s, 24 H), 9.45 (s, 8 H), 9.50 (s, 8 H).

4. [5,10,15,20-Tetrakis(1,2-dimethylpyrazolium-4-yl)porphyrinato]manganese(III) Pentachloride (52).

Porphyrin 51 (40 mg, 4.80 x 10^{-2} mmol) was dissolved in water (10 mL). Manganese (II) chloride (90 mg, 0.72 mmol) was added and the reaction was heated at 50 °C. Analysis of the reaction mixture by UV-vis spectroscopy showed incomplete reaction. Additional $MnCl_2$ (210 mg, 1.67 mmol) was added and heating of the reaction mixture was continued until completion of reaction was indicated by UV-vis analysis. Filtration followed by purification of the product by the double precipitation method provided porphyrin 52 (25 mg, 57%) as a brown solid: mp >300 °C; UV-vis λ_{max} = 461.0 nm.

ε = 7.82 x 10^4 L/cm-mol; API MS *m/z* = 683 $[C_{40}H_{40}MnN_{12} - 4CH_3]^+$.

XIV. [5,10,15,20-Tetrakis(1,3-dimethylimidazolium-5-yl)porphyrinato]manganese(III) Pentachlorid (56).



1. 5,10,15,20-Tetrakis(1-methylimidazol-5-yl)porphyrin (54).

To a refluxing solution of propionic acid (400 mL) and 1-methylimidazole-5-carboxaldehyde (53, 2.0 g, 18.16 mmol), prepared according to literature procedure (Dener, J. M.; Zhang, L-H.; Rapoport, H. *J. Org. Chem.* 1993, *58*, 1159-1166), was added pyrrole (1.26 mL, 18.16 mmol). The reaction was covered with foil then heated under reflux for 5 h. Upon cooling, the reaction mixture was exposed to air for 60 h. The propionic acid was then removed by vacuum distillation. The residue was dissolved in 10% MeOH/CH_2Cl_2, then adsorbed onto silica gel (6 g). Purification by column chromatography (gradient elution, 5-10% MeOH/CH_2Cl_2) provided porphyrin 54 as a purple solid (600 mg, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) δ -2.80,-2.75 (2 s, 2 H, atropisomer NH), 3.42-3.58 (multiple s, 12 H, atropisomer N-CH_3), 7.87-7.98 (multiple s, 4 H, atropisomer), 8.06 (s, 4 H), 8.95-8.99 (multiple s, 8 H, atropisomer).

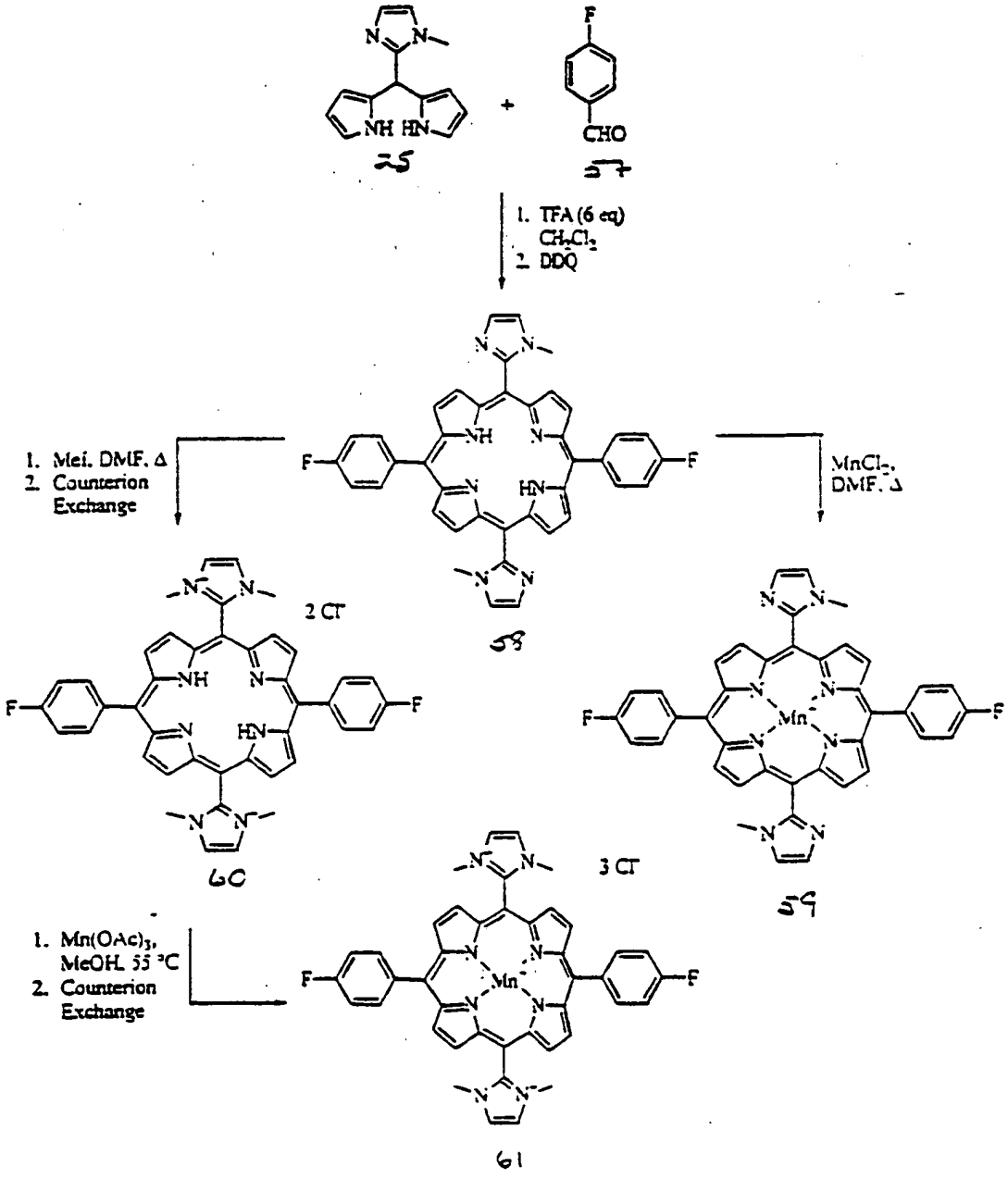
2. 5,10,15,20-Tetrakis(1,3-dimethylimidazolium-5-yl)porphyrin Tetraiodide (55).

Porphyrin 54 (395 mg, 0.63 mmol) was dissolved in DMF (15 mL) in a sealed tube reactor. Methyl iodide (2 mL, 32 mmol) was added and the sealed tube was heated at 100 °C overnight. Dilution of the reaction mixture with EtOAc (200 mL) resulted in the precipitation of the crude product which was collected by vacuum filtration. Purification by column chromatography (8:1:1 CH_3CN/water/saturated KNO_3) provided porphyrin 55 (250 mg, 33%) as a dark purple solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ -3.25 (s, 2 H), 3.46-3.64 (multiple s, 12 H, atropisomer), 4.30 (s, 12 H), 8.68 (s, 4 H), 9.48 (s, 8 H), 9.78 (s, 4 H).

3. [5,10,15,20-Tetrakis(1,3-dimethylimidazolinm-5-yl)porphyrinato]-manganese(III) Pentachloride (56).

Porphyrin 55 (200 mg, 0.17 mmol) was dissolved in methanol (100 mL). Manganese (II) chloride (315 mg, 2.50 mmol) was added and an air stream introduced into the reaction mixture. The pH of the solution was maintained at 8 by the dropwise addition of 6N NaOH over the period of the reaction, after which time the pH was adjusted to 5 with 6N HCl. The reaction was filtered on a fritted funnel. Purification of the product by the double precipitation method provided porphyrin 56 (63 mg, 41%) as a brown solid: mp >300 °C; UV-vis λ_{max} = 454.0 nm, ε = 1.23 x 10^5 L/cm-mol.

XV. [5,15-Bis(4-fluorophenyl)-10,20-bis(1-methylimidazol-2-yl)porphyrinato]-manganese(III) Chloride (59) and [5,15-Bis(4-fluorophenyl)-10,20-bis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Trichloride (61).



1. 5,15-Bis(4-fluorophenyl)-10,20-bis(1-methylimidazol-2-yl)porphyrin (58). In a foil-covered 1-L three-neck round bottom flask equipped with a magnetic stirrer and a N_2 outlet, was added dipyrromethane 25 (1.00 g, 4.43 mmol), 4-fluorobenzaldehyde (57, 550 mg, 4.43 mmol), sodium chloride (30 mg, 0.5 mmol) and CH_2Cl_2 (450 mL). The reaction mixture was stirred for 10 min, then TFA (2.0 mL, 26 mmol) was added. After a stirring period of 105 min, DDQ (1.51 g, 6.65 mmol) was added, and the mixture was stirred overnight. The solvent was removed by rotary evaporation, and the crude residue was adsorbed onto silica gel (3 g). Purification by column chromatography (gradient elution, 5-10% MeOH/CH_2Cl_2) provided porphyrin 58 (229 mg, 16%) as a black solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ -3.05 (s, 2 H), 3.70, 3.72 (2 s, 6 H, atropisomer N-CH_3), 7.73 (m, 8 H), 8.19 (s, 2 H), 8.30 (m, 4 H), 9.02 (m, 6 H); API-MS *m/z* = 659 [$C_{40}H_{28}F_2N_8$ + H]$^+$.

2. [5,15-Bis(4-fluorophenyl)-10,20-bis(1-methylimidazol-2-yl)porphyrinato]-manganese(III) Chloride (59). Porphyrin 58 (85 mg, 0.13 mmol) was dissolved in DMF (7 mL) in a 50-mL round bottom flask equipped with a condenser. Manganese (II) chloride (215 mg, 1.71 mmol) was added and the reaction was heated at 120 °C for 3.5 h. The reaction was cooled to room temperature then concentrated by rotary evaporation. The crude residue was dissolved in 20% MeOH/CH_2Cl_2 (100 mL) and adsorbed onto silica gel (2 g). Purification by column chromatography (gradient elution, 3-8% MeOH/CH_2Cl_2) provided porphryin 59 as a green solid (15 mg, 16%): mp >300 °C; UV-vis λ_{max} = 463.0 nm, ε = 4.05 x 10^4 L/cm-mol; API MS *m/z* = 711 [$C_{40}H_{26}F_2MnN_8$]$^+$.

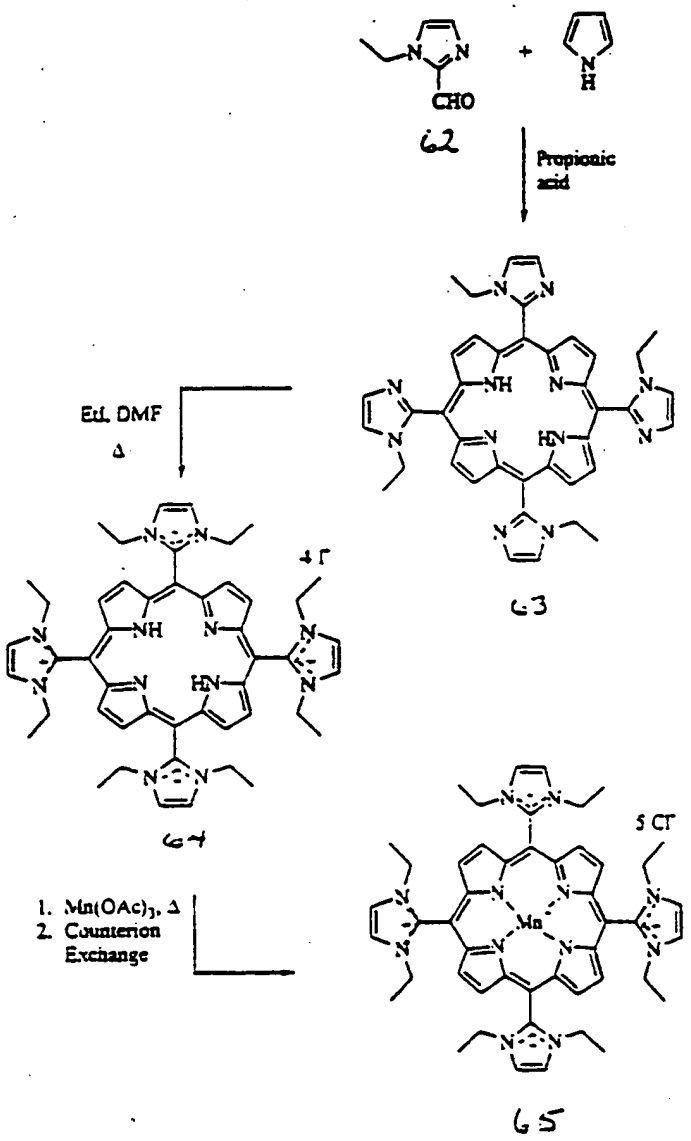
3. 5,15-Bis(4-fluorophenyl)-10,20-bis(1,3-imidazolium-2-yl)porphyrin Dichl ride (60).

Porphyrin **58** (170 mg, 0.26 mmol) was dissolved in DMF (7 mL) in a sealed tube reactor. Methyl iodide (6 mL, 96 mmol) was added and the sealed tube was heated at 100 °C overnight. The mixture was cooled to room temperature and concentrated by rotary evaporation. The residue was precipitated as the chloride salt from acetone by the addition of Bu_4NCl solution in acetone (0.3 g/mL). The solid was collected on a fritted funnel, washed with copious quantities of acetone, and dried under vacuum at room temperature to provide porphyrin **60** as a dark purple solid (196 mg). The product was used without further purification.

4. [5,15-Bis(4-fluorophenyl)-10,20-bis(1,3-dimethylimidazolium-2-yl)porphyrinato]manganese(III) Trichloride (61).

Porphyrin **60** (196 mg, est. 0.26 mmol) dissolved in MeOH (30 mL) was slowly warmed to 55 °C then $Mn(OAc)_3 \cdot 2\ H_2O$ (694 mg, 2.59 mmol) was added. After a stirring period of 3 h, the mixture was cooled to room temperature, filtered through Celite and concentrated by rotary evaporation. The residue was purified by the double precipitation method to provide porphyrin **61** (102 mg, 46% over two steps) as a dark green solid: mp >300 °C, UV-vis λ_{max} = 458.0 nm; $\varepsilon = 1.30 \times 10^5$ L/cm-mol; ES-MS *m/z* = 967 $[(C_{42}H_{32}F_2MnN_8)^{+3} + 2\ (CF_3CO_2^-)]^+$.

XVI. [5,10,15,20-Tetrakis(1,3-diethylimidazolium-2-yl)porphyrinat]manganese(III) Pentachloride (65).



1. 5,10,15,20-Tetrakis(1-ethylimidazol-2-yl)porphyrin (63).

To a refluxing solution of propionic acid (450 mL) and 1-ethylimidazole-2-carboxaldehyde (62, 2.5 g, 20.0 mmol, prepared in a similar manner as the methyl imidazole derivative 20) was added pyrrole (1.40 mL, 20.0 mmol). The reaction was covered in foil then heated under reflux for 5 h. Upon cooling, the reaction mixture was exposed to air overnight. The propionic acid was then removed by vacuum distillation. Repeated purification by column chromatography (gradient elution, $CHCl_3$/MeOH/ concentrated NH_4OH/EtOAc) provided porphyrin 63 as a purple solid (281 mg, 8.1%): ^1H NMR (300 MHz, $CDCl_3$) δ -2.95,-2.90, -2.87 (3 s, 2 H, atropisomer NH), 0.85-1.25 (multiple t, 12 H, atropisomer CH_3), 3.61-3.88 (multiple q, 8 H, atropisomer CH_2), 7.55 (d, 4 H), 7.70 (d, 4 H), 8.98 (multiple s, 8 H, atropisomer).

2. 5,10,15,20-Tetrakis(1,3-diethylimidazolium-2-yl)porphyrin Tetraiodide (64).

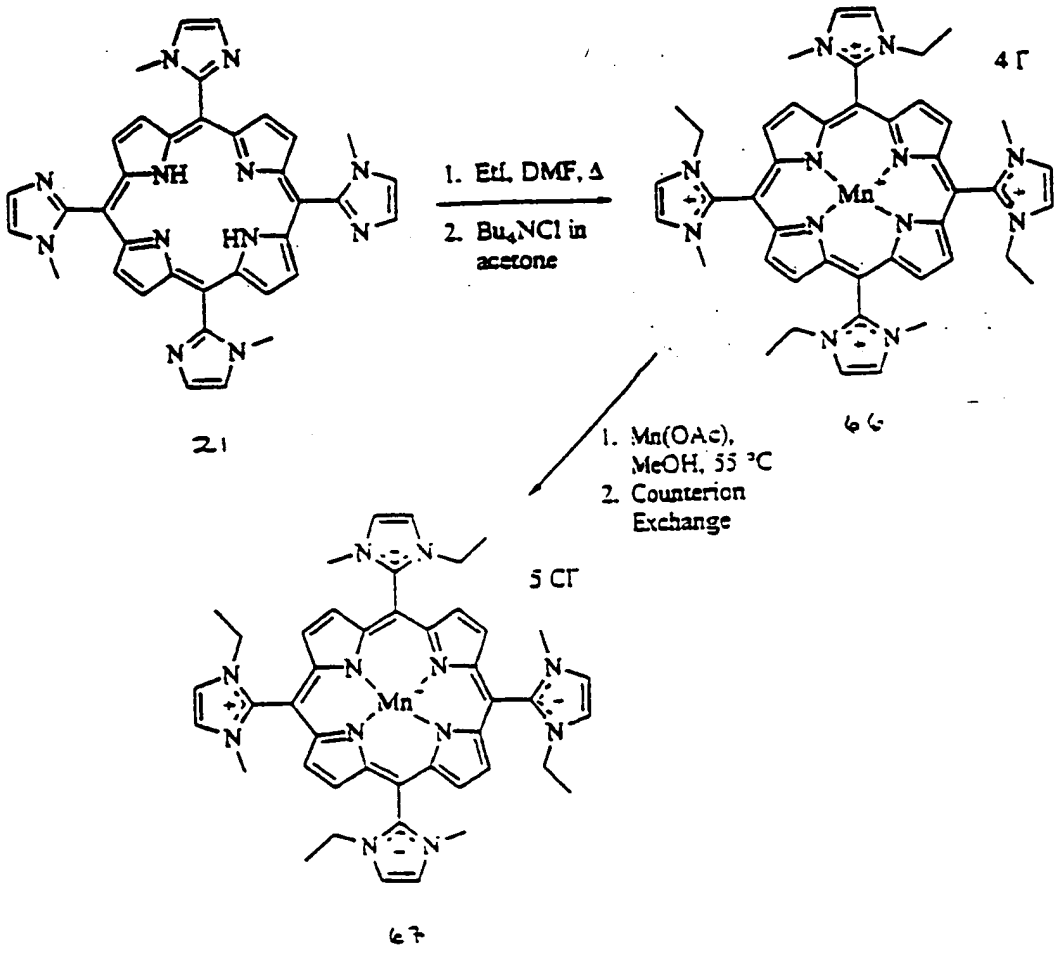
Porphyrin 63 (106 mg, 0.15 mmol) was dissolved in DMF (5 mL) in a sealed tube reactor. Ethyl iodide (2.0 mL, 25 mmol) was added and the sealed tube was heated at 65 °C for 6 h. Dilution of the reaction mixture with EtOAc (100 mL) resulted in the precipitation of the crude product which was collected by vacuum filtration, washed with chloroform and then purified by column chromatography (8:1:1 CH_3CN/water/saturated KNO_3) to provide porphyrin 63 (140 mg, 69%) as a dark purple solid: ^1H NMR (300 MHz, DMSO-d_6) δ -3.22 (s, 2 H), 1.17 (t, 24 H), 4.01 (s, 16 H), 8.70 (s, 8 H), 9.43 (s, 8 H).

3. [5,10,15,20-Tetrakis(1,3-diethylimidazolium-2-yl)porphyrinato]-manganese(III) Pentachloride (65).

Porphyrin 64 (106 mg, 8.09 x 10^{-2} mmol) was dissolved in methanol (15 mL) then $Mn(OAc)_3 \cdot 2\ H_2O$ (216 mg, 0.81 mmol) was added and the reaction heated at 55 °C

for 2.5 h. The reaction was filtered through celite and then evaporated *in vacuo*. Purification of the product by the double precipitation method provided porphyrin 65 (65 mg, 78%) as a brown solid: mp >300 °C, UV-vis λ_{max} = 446.5 nm, ε = 1.35 x 10^5 L/cm-mol; ES-MS *m/z* = 1307 $[(C_{48}H_{28}MnN_{12})^{+1} + 4(CF_3CO_2^-)]^-$.

XVII. [5,10,15,20-Tetrakis(1-ethyl-3-methylimidazolium-2-yl)porphyrinato]-manganese(III) Pentachloride (67).



21 66 67

1. 5,10,15,20-Tetrakis(1-ethyl-3-methylimidazolium-5-yl)porphyrin Tetrachloride (66).

Porphyrin 21 (371 mg, 0.588 mmol) was dissolved in DMF (8 mL) in a sealed tube reactor. Ethyl iodide (7 mL, 88 mmol) was added and the sealed tube was heated at 60 °C overnight. The mixture was cooled to room temperature and concentrated by rotary evaporation. The residue was dissolved in water (20 mL) and purified by the double precipitation method to provide porphyrin 66 (349 mg, 67%) as a dark

purple solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ -3.23 (s, 2 H), 1.17 (m, 12 H), 3.77 (m, 12 H), 4.03 (m, 8 H), 7.01, 7.18, 7.35 (multiple s, 8 H), 8.63 (d, 4 H), 9.36 (s, 4 H).

2. [5,10,15,20-Tetrakis(1-ethyl-3-methylimidazolium-2-yl)porphyrinato]-manganese(III) Pentachloride (67).

Porphyrin **66** (340 mg, 0.39 mmol) was dissolved in methanol (45 mL) then $Mn(OAc)_3 \bullet 2\ H_2O$ (680 mg, 2.53 mmol) was added, and the mixture was stirred at 55 °C for 3.5 h. The mixture was cooled to room temperature, filtered through Celite (to remove insoluble solids), and concentrated by rotary evaporation. The residue was purified by the double precipitation method to provide porphyrin **67** (324 mg, 85%) as a brown solid: mp >300 °C; UV-vis λ_{max} = 446.5 nm; e = 5.11 x 10^4 L/cm-mol; ES-MS *m/z* = 1251 $[(C_{44}H_{48}MnN_{12})^{+5} + 4\ (CF_3CO_2^-)]^+$.

EXAMPLE 2

Treatment of Bronchopulmonary Dysplasia Using Aeol-V (10123)

Neonatal baboons were delivered prematurely by Caesarian section and then treated either with 100% oxygen or only sufficient PRN FIO_2 to maintain adequate arterial oxygenation. To establish the model, thirteen 100% oxygen treated animals and seven PRN control animals were studied. Treatment with 100% oxygen results in extensive lung injury manifested by days 9 or 10 of exposure and characterized by delayed alveolarization, lung parenchymal inflammation, and poor oxygenation. This is characteristic of the human disease, bronchopulmonary dysplasia, and is thought to be mediated, at least in part, by oxidative stress on the developing neonatal lung. In a first trial of Aeol-V, a neonatal baboon was delivered at 140 days gestation and placed in 100% oxygen. The animal received 0.25 mg/kg/24 hr given i.v. in a continuous infusion over the entire 10 day study period (see Fig. 2).

This animal showed marked improvement of the oxygenation index. There was no evidence of clinical decompensation of the lungs at days 9 and 10. This suggests that Aeol-V can be used to treat oxidant stress in the premature newborn.

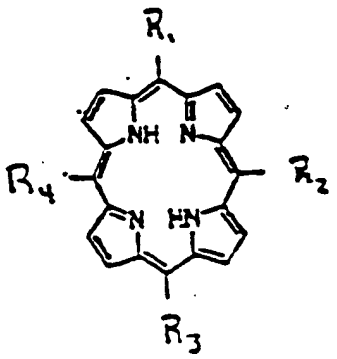
* * * * *

All documents cited above are hereby incorporated in their entirety by reference.

One skilled in the art will appreciate from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention.

WHAT IS CLAIMED IS:

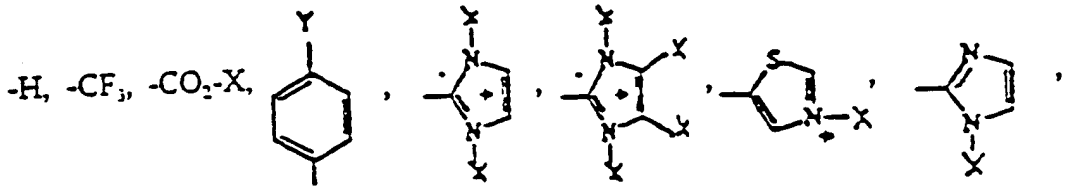
1. A compound of formula



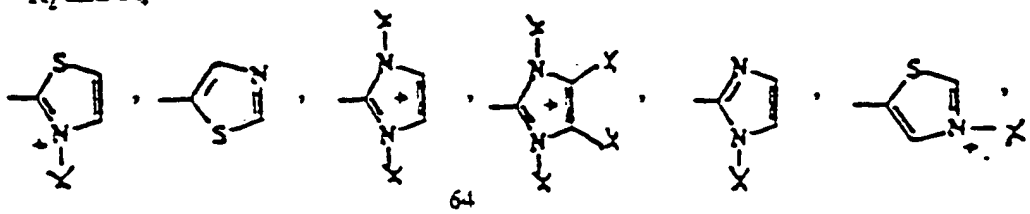
or pharmaceutically acceptable salt thereof.

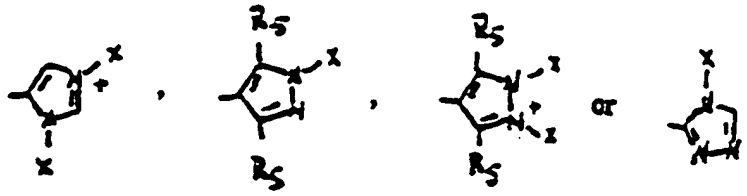
wherein

R_1 and R_3 are the same and are:



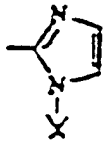
R_2 and R_4 are the same and are :

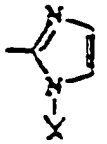




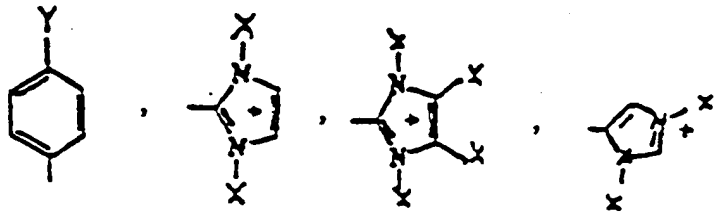
Y is halogen or $-CO_2X$, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl.

wherein when R_1 and R_2 are -H, R_3 and R_4 are not  . or

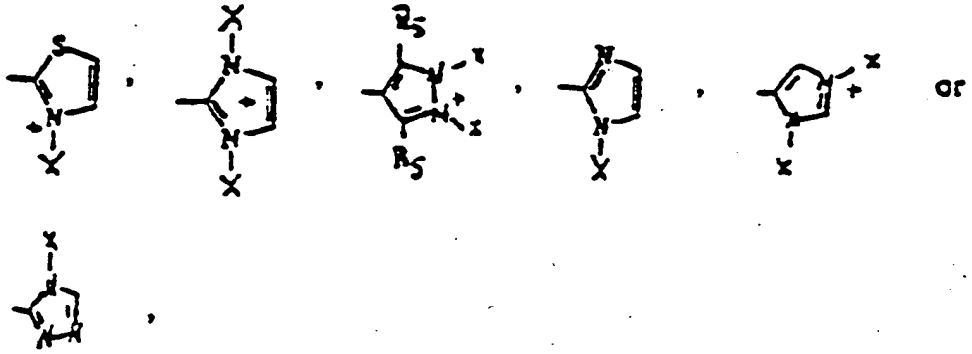
when R_1 and R_3 are -H, and R_2 and R_4 are  , said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt or nickel.

2. The compound according to claim 1 wherein R_1 and R_3 are the same and are:

-H, CF_3, $-CO_2-X$, 

or  ,

R_2 and R_4 are the same and are :



or

Y is -F or $-CO_2X$, and

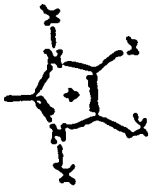
X is the same or different and is a C_{1-4} alkyl and each R_5 is the same or different and is H or C_{1-4} alkyl.

3. The compound according to claim 2 wherein X is methyl or ethyl.

4. The compound according to claim 1 wherein R_1, R_2, R_3 and R_4 are the same.

5. The compound according to claim 1 wherein R_1, R_2, R_3 and R_4 are

or



o. The compound according to claim 5 wherein X is methyl or ethyl.

7. The compound according to claim 5 wherein R_1, R_2, R_3 and R_4 are the same.

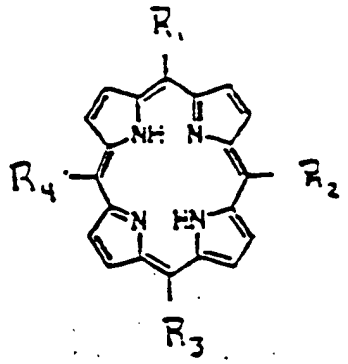
8. The compound according to claim 7 wherein R_1, R_2, R_3 and R_4 are

.

9. The compound according to claim 1 wherein said compound is complexed with a metal selected from the group consisting of zinc, iron, nickel, cobalt, copper, manganese.

10. The compound according to claim 9 wherein said compound is complexed with manganese.

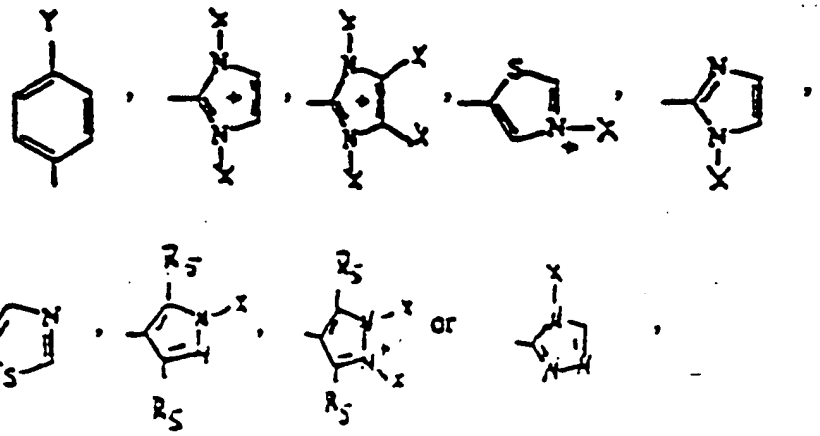
11. A method of protecting cells from oxidant- induced toxicity comprising contacting said cells with a protective amount of a compound of formula



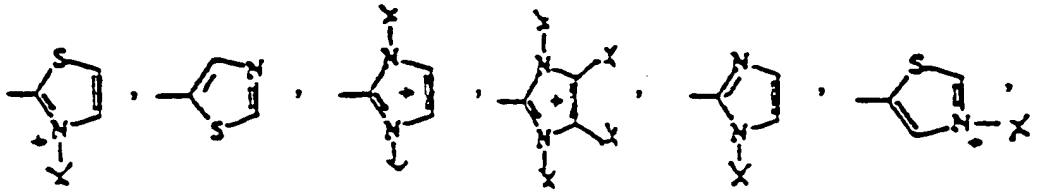
or pharmaceutically acceptable salt thereof,

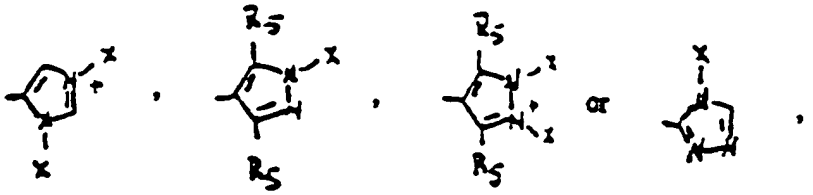
wherein

R_1 and R_3 are the same and are:

-H, $-CF_3$, $-CO_2-X$, 

R_2 and R_4 are the same and are :





Y is halogen or $-CO_2X$, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said protection is effected.

12. The method according to claim 11 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

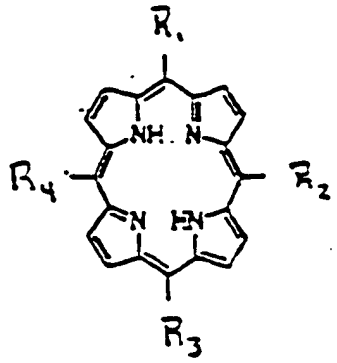
13. The method according to claim 12 wherein said metal is manganese.

14. The method according to claim 11 wherein said cells are mammalian cells.

15. The method according to claim 14 wherein said cells are cells of an isolated organ.

16. The method according to claim 14 wherein said cells are cells of an organ transplant.

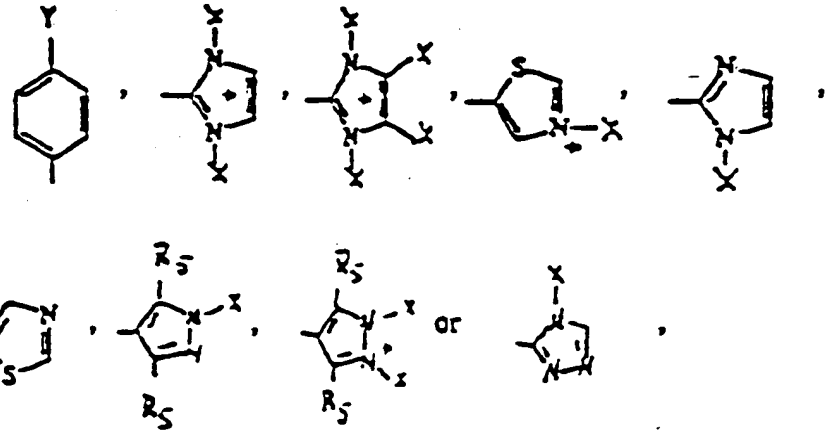
17. A method of treating a patient suffering from a condition that results from or that is exacerbated by oxidant-induced toxicity comprising administering to said patient an effective amount of a compound of formula



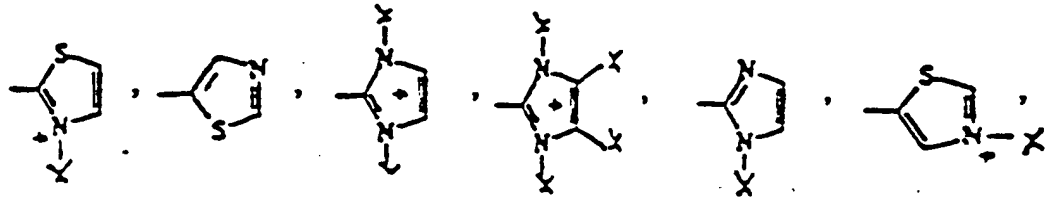
or pharmaceutically acceptable salt thereof,

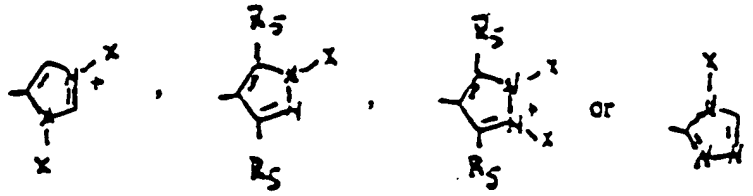
wherein

R_1 and R_3 are the same and are:

-H, $-CF_3$, $-CO_2-X$, 

R_2 and R_4 are the same and are :





Y is halogen or $-CO_2X$, and

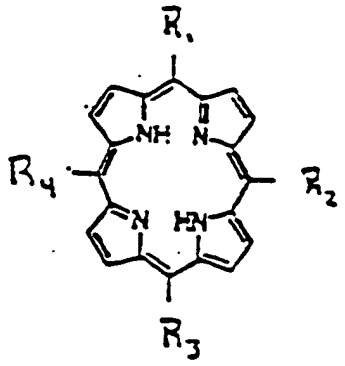
X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

18. The method according to claim 17 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

19. The method according to claim 18 wherein said compound is complexed with manganese.

20. A method of treating a pathological condition of a patient resulting from degradation of $NO^{\cdot}$ or a biologically active form thereof, comprising administering to said patient an effective amount of a compound of formula



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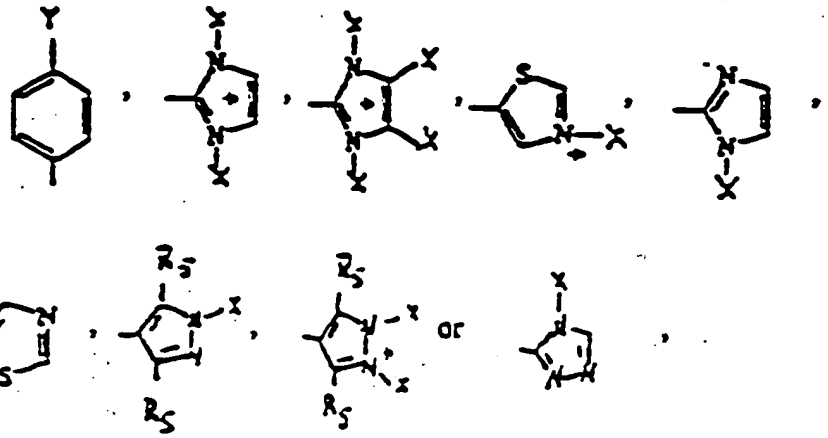
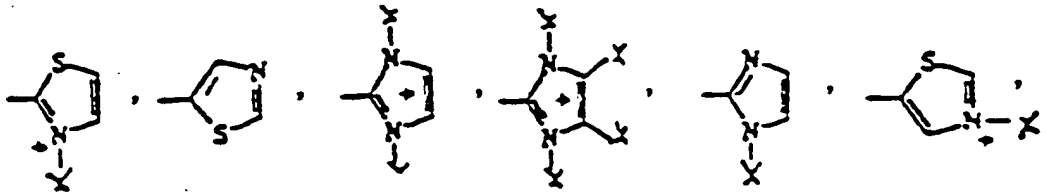
or pharmaceutically acceptable salt thereof,

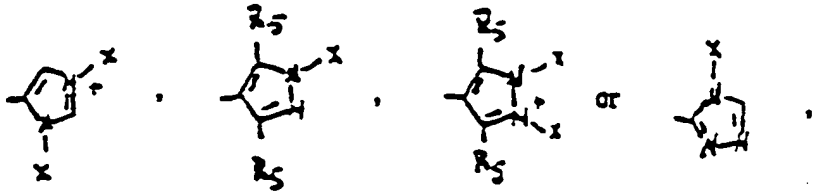
wherein

R_1 and R_3 are the same and are:

-H, $-CF_3$, $-CO_2-X$, 

R_2 and R_4 are the same and are :





Y is halogen or $-CO_2X$, and

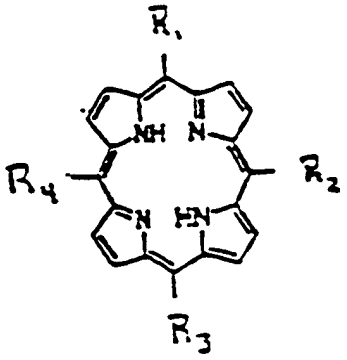
X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

21. The method according to claim 20 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

22. The method according to claim 21 wherein said compound is complexed with manganese.

23. A method of treating a patient for an inflammatory disease comprising administering to said patient an effective amount of a compound of formula

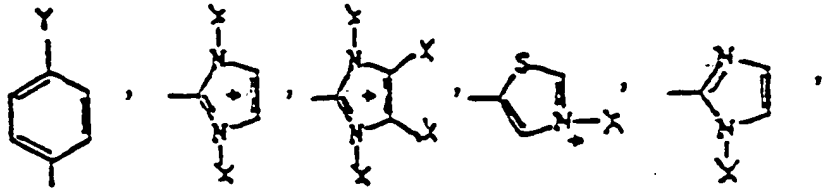


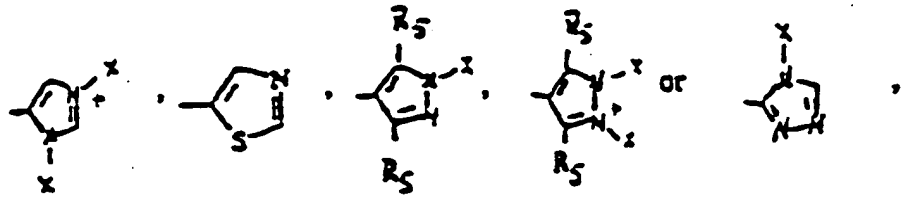
I

or pharmaceutically acceptable salt thereof.

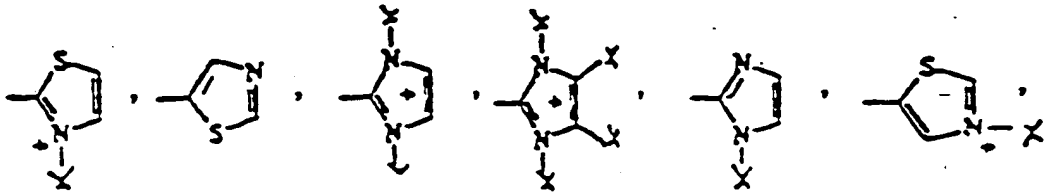
wherein

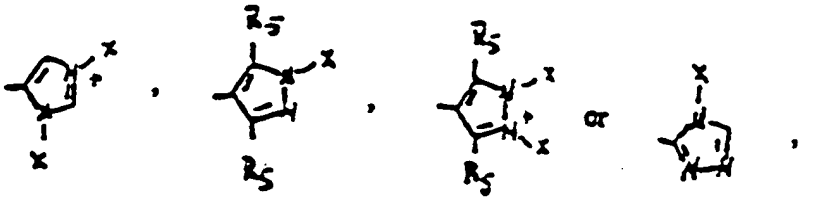
R_1 and R_3 are the same and are:

-H, -CF_3, -CO_2-X, 



R_2 and R_4 are the same and are :





Y is halogen or $-CO_2X$, and

X is the same or different and is an alkyl and each R_5 is the same or different and is H or alkyl,

so that said treatment is effected.

24. The method according to claim 23 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

25. The method according to claim 24 wherein said compound is complexed with manganese.

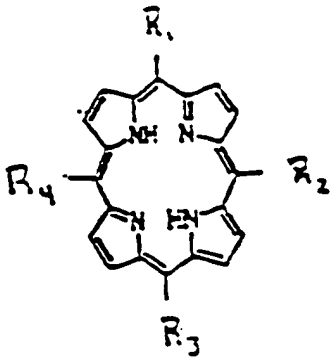
26. The method according to claim 23 wherein said inflammatory disease is an inflammatory lung disease.

27. The method according to claim 26 wherein said inflammatory lung disease is bronchopulmonary disease.

28. The method according to claim 26 wherein said inflammatory lung disease is asthma.

29. The method according to claim 26 wherein said inflammatory lung disease is pulmonary fibrosis.

30. A method of treating a patient for an ischemic reperfusion injury comprising administering to said patient an effective amount of a compound of formula



I

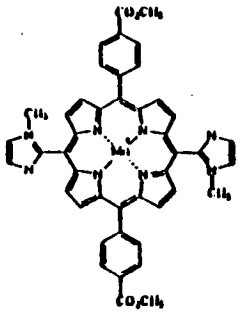
or pharmaceutically acceptable salt thereof.

31. The method according to claim 30 wherein said compound is complexed with a metal selected from the group consisting of manganese, iron, copper, cobalt, nickel or zinc.

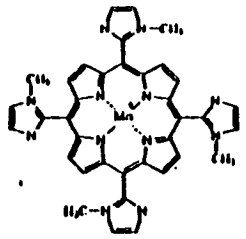
32. The method according to claim 31 wherein said compound is complexed with manganese.

33. The method according to claim 30 wherein said ischemic reperfusion injury results from a stroke.

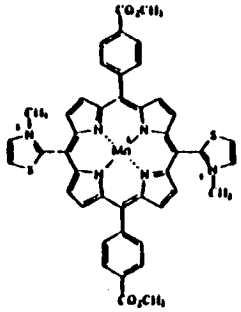
Figure 1 A



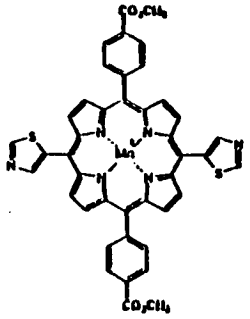
Acol-10118



Acol-10119

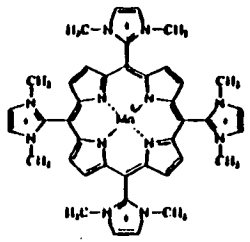


Acol-10121

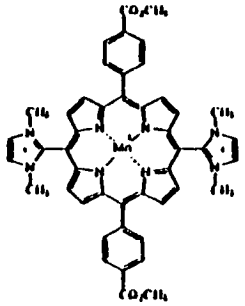


Acol-10122

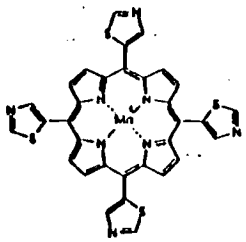
SOD	13	interferes	164	19
CAT	0.16	0.14	0.32	0.3
TBARS	20	27	2	4



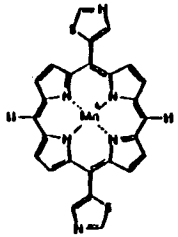
Acol-10123



Acol-10124



Acol-10125

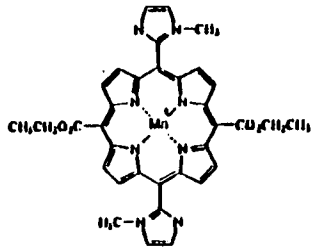


Acol-10127

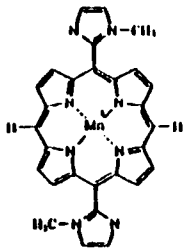
SOD	16,600	5	interferes	interferes
CAT	2.56	0.44	0.04	0.1
TBARS	2	2	16	10

2

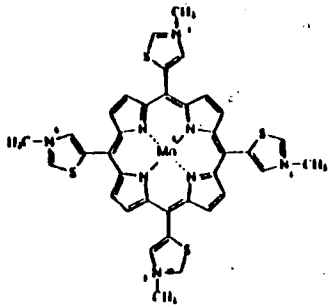
Figure 1 B



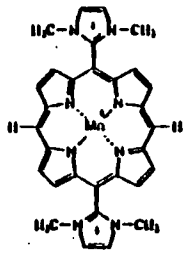
Acol-10128



Acol-10130

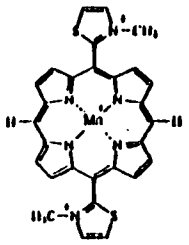


Acol-10131

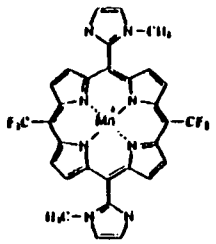


Acol-10133

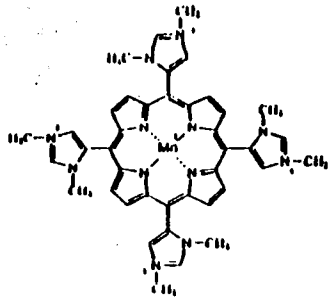
SOD	interferes	3	interferes	31
CAT	0.04	0.16	2.6	2.1
TBARS	1	2	4	2



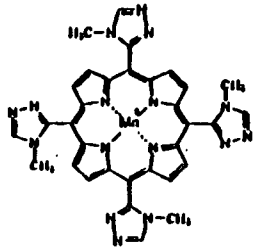
Acol-10134



Acol-10135



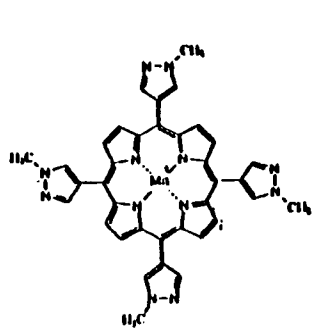
Acol-10136



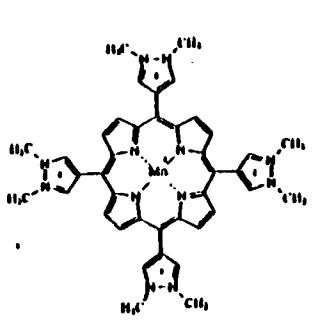
Acol-10138

SOD	interferes	16	1900	56
CAT	1.3	0.02	1.8	0.23
TBARS	2	2	13	2

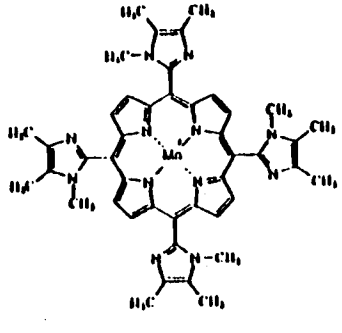
Figure 1C



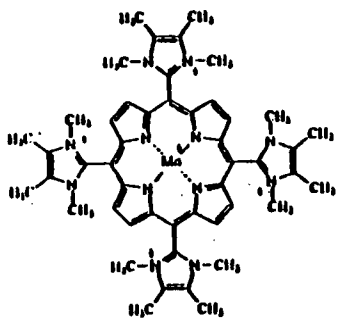
Acol-10139



Acol-10141

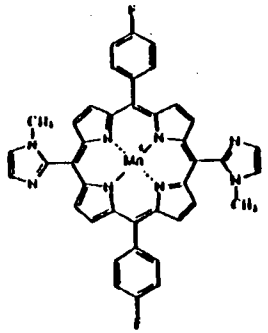


Acol-10142

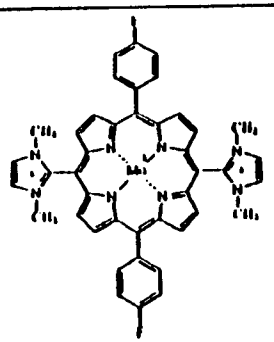


Acol-10143

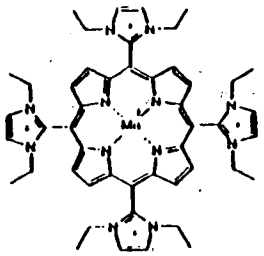
SOD	interferes	77	INTERFERES	13,400
CAT	0.76	1.46	NOT DONE	NOT DONE
TBARS	.21	77	NOT DONE	NOT DONE



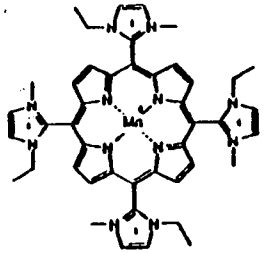
Acol-10145



Acol-10149



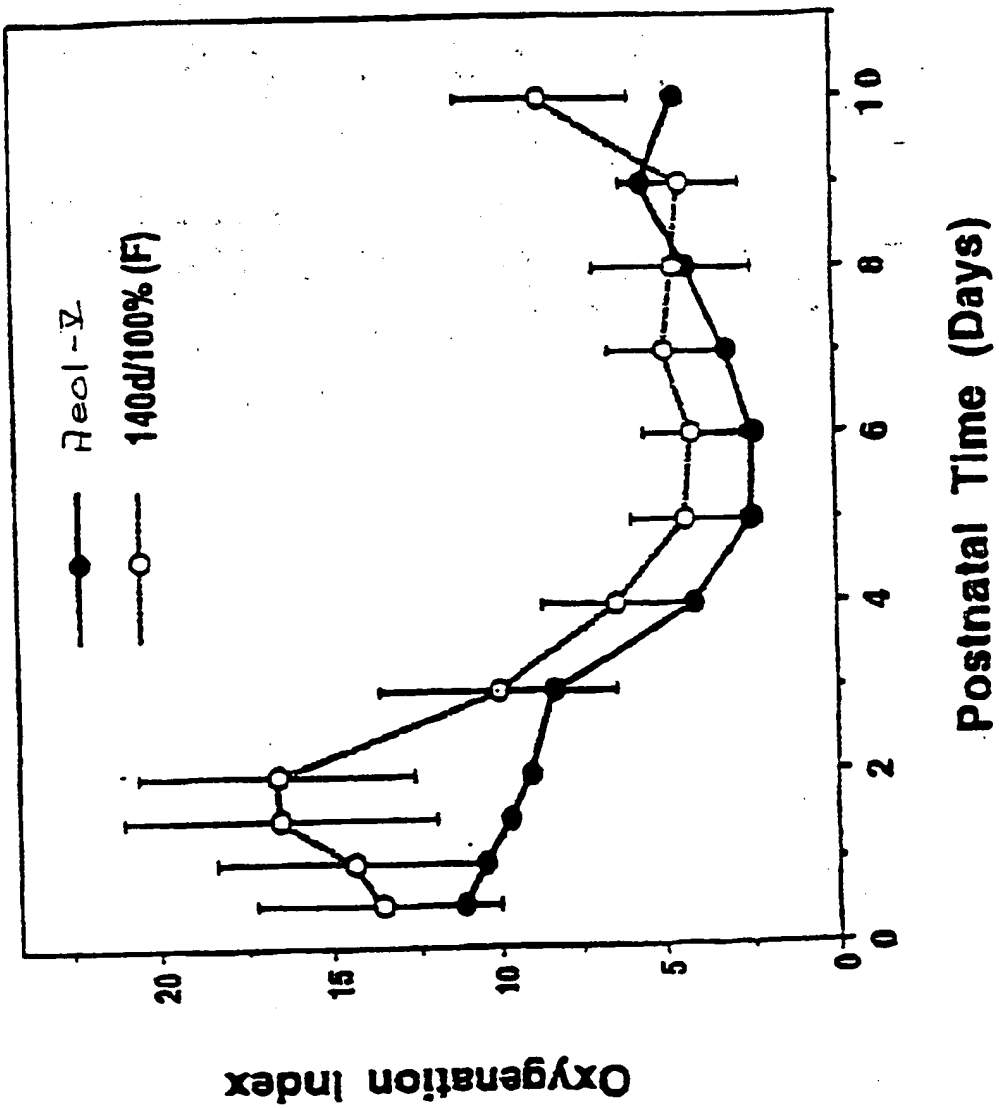
Acol-10150



Acol-10151

SOD	16	121	13,887	6260
CAT	NOT DONE	NOT DONE	NOT DONE	NOT DONE
TBARS	NOT DONE	NOT DONE	NOT DONE	NOT DONE

Figure 2


Oxygenation Index
Postnatal Time (Days)
Reol-Z
140d/100% (F)
0
5
10
15
20
0
2
4
6
8
10

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/02062

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C07D 487/22; C09B 47/00; A61K 51/02

US CL :514/183,184; 540/145

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/183,184; 540/145

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,885,114 A (GORDON et al.,) 05 December 1989, col 10, lines 5-60	1-33
Y	US 5,236,914 A (MEUNIER et al) 17 August 1993, abstract	1-33

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 MARCH 2000	Date of mailing of the international search report 19 MAY 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer PK SRIPADA Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet) (July 1998)*